Medical Policy

Blue Cross Blue Shield Blue Care Network of Michigan

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Title: Orthopedic Applications of Platelet-Rich Plasma

Description/Background

A variety of growth factors have been found to play a role in wound healing, including platelet-derived growth factors, epidermal growth factor, fibroblast growth factors, transforming growth factors, and insulin-like growth factors. Autologous platelets are a rich source of platelet-derived growth factor, transforming growth factors that function as a mitogen for fibroblasts, smooth muscle cells, osteoblasts, and vascular endothelial growth factors. Recombinant platelet-derived growth factor, has also been extensively investigated for clinical use in wound healing (see policy: “Platelet Rich Plasma Autologous Platelet-Derived Growth Factors as a Treatment of Wound Healing and Other Non-Orthopedic Conditions”).

Autologous platelet concentrate suspended in plasma, also known as platelet-rich plasma (PRP), can be prepared from samples of centrifuged autologous blood. Exposure to a solution of thrombin and calcium chloride degranulates platelets, releasing the various growth factors. The polymerization of fibrin from fibrinogen creates a platelet gel, which can then be used as an adjunct to surgery with the intent of promoting hemostasis and accelerating healing. In the operating room setting, PRP has been investigated as an adjunct to various periodontal, reconstructive, and orthopedic procedures. For example, bone morphogenetic proteins are a type of transforming growth factors, and thus PRP has been used in conjunction with bone-replacement grafting (using either autologous grafts or bovine-derived xenograft) in periodontal and maxillofacial surgeries. Alternatively, PRP may be injected directly into various tissues. PRP injections have been proposed as a primary treatment of miscellaneous conditions, such as epicondylitis, plantar fasciitis, and Dupuytren contracture.

Injection of PRP for tendon and ligament pain is theoretically related to prolotherapy (see policy: “Prolotherapy”). However, prolotherapy differs in that it involves injection of chemical irritants intended to stimulate inflammatory responses and induce release of endogenous growth factors.

PRP is distinguished from fibrin glues or sealants, which have been used as a surgical adjunct to promote local hemostasis at incision sites. Fibrin glue is created from platelet-poor plasma and consists primarily of fibrinogen. Commercial fibrin glues are created from pooled homologous human donors; Tisseel® (Baxter) and VITASEAL™ (Johnson & Johnson Surgical Technologies) are examples of commercially available fibrin sealants. Autologous fibrin sealants can be created from platelet-poor plasma. This evidence review does not address the use of fibrin sealants.

Regulatory Status

The U.S. Food and Drug Administration (FDA) regulates human cells and tissues intended for implantation, transplantation, or infusion through the Center for Biologics Evaluation and Research, under Code of Federal Regulation (CFR) title 21, parts 1,270 and 1,271. Blood products such as platelet-rich plasma are included in these regulations. Under these regulations, certain products including blood products such as platelet-rich plasma are exempt and therefore do not follow the traditional FDA regulatory pathway. To date, the FDA has not attempted to regulate activated platelet-rich plasma.

A number of platelet-rich preparation systems are available, many of which were cleared for marketing by FDA through the 510(k) process for producing platelet-rich preparations intended to be mixed with bone graft materials to enhance the bone grafting properties in orthopedic practices. The use of platelet-rich plasma outside of this setting (eg, an office injection) would be considered off-label. The Aurix System®™ (previously called AutoloGel™; Nuo Therapeutics) and SafeBlood® (SafeBlood Technologies) are 2 related but distinct autologous blood-derived preparations that can be used at the bedside for immediate application. Both AutoloGel™ and SafeBlood® have been specifically marketed for wound healing. Other devices may be used during surgery (eg, autoLog® Autotransfusion system[Medtronic], the SmartPReP [Harvest Technologies] device). The Magellan®™ Autologous Platelet Separator System (Isto Biologics) includes a disposable kit for use with the Magellan™ Autologous Platelet Separator portable tabletop centrifuge. GPS®II (BioMet Biologics), a gravitational platelet separation system, was cleared for marketing by the FDA through the 510(k) process for use as disposable separation tube for centrifugation and a dual cannula tip to mix the platelets and thrombin at the surgical site (GPS® III [Zimmer Biomet] is now available). Filtration or plasmapheresis may also be used to produce platelet-rich concentrates. Regen lab® USA received its first FDA clearance in May 2010 with RegenKit® THT®, [62] which is a member of a family of medical devices that have been manufactured in the United States since November 2021. RegenKit technology allows for a rapid standardized PRP preparation process with a closed-circuit system. The use of different devices and procedures can lead to variable concentrations of active platelets and associated proteins, increasing variability between studies of clinical efficacy.

Medical Policy Statement

Use of platelet-rich plasma is considered experimental/investigational for all orthopedic indications. It has not been scientifically demonstrated to improve patient clinical outcomes.

Inclusionary and Exclusionary Guidelines

Exclusions

Use of platelet-rich plasma is considered experimental/investigational for all orthopedic indications. This includes, but is not limited to, use in the following situations:

Primary use (injection) for the following conditions:

- Achilles tendinopathy
- Lateral epicondylitis
- Osteochondral lesions
- Osteoarthritis
- Plantar fasciitis

Adjunctive use in the following surgical procedures:

- ACL reconstruction
- Hip fracture
- Long-bone nonunion
- Patellar tendon repair
- Rotator cuff repair
- Spinal fusion
- Subacromial decompression surgery
- Total knee arthroplasty

CPT/HCPCS Level II Codes *(Note: The inclusion of a code in this list is not a guarantee of coverage. Please refer to the medical policy statement to determine the status of a given procedure.)*

Established codes:

N/A

Other codes (investigational, not medically necessary, etc.):

0232T C1734

Rationale

Evidence reviews assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are length of life, quality of life, and ability to function, including benefits and harms. Every clinical condition has specific outcomes that are important to patients and to managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of a technology, 2 domains are examined: the relevance, and quality and credibility. To be relevant, studies must represent 1 or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. RCTs are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

At present, there are a large number of techniques available for the preparation of platelet-rich plasma or platelet-rich plasma gel. The amount and mixture of growth factors produced by different cell-separating systems vary, and it is also uncertain whether platelet activation before the injection is necessary.[1,2,3,4,5,6]

PLATELET-RICH PLASMA AS A PRIMARY TREATMENT FOR TENDINOPATHY

Clinical Context and Therapy Purpose

The purpose of platelet-rich plasma injections is to provide a treatment option that is an alternative to or an improvement on existing therapies, such as nonpharmacologic therapy (eg, exercise, physical therapy), analgesics, and anti-inflammatory agents in individuals with tendinopathy.

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is individuals with tendinopathy.

Interventions

The therapy being considered is platelet-rich plasma injections. The use of platelet-rich plasma has been proposed as a treatment for various musculoskeletal conditions and as an adjunctive procedure in orthopedic surgeries. The potential benefit of platelet-rich plasma has received considerable interest due to the appeal of a simple, safe, low-cost, and minimally invasive method of applying growth factors.

Comparators
Comparators of interest include nonpharmacologic therapy (eg, exercise, physical therapy), analgesics, and anti-inflammatory agents.

Outcomes
The general outcomes of interest are symptoms, functional outcomes, health status measures, quality of life, and treatment-related morbidity. The existing literature evaluating platelet-rich plasma injections as a treatment for tendinopathy has varying lengths of follow-up, ranging from 6 months to 2 years. While studies described below all reported at least 1 outcome of interest, longer follow-up is necessary to fully observe outcomes.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:

a. To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
b. In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
c. To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
d. Studies with duplicative or overlapping populations were excluded.

REVIEW OF EVIDENCE

Systematic Reviews

Many systematic reviews have evaluated platelet-rich plasma for treating mixed tendinopathies. They include trials on tendinopathies of the Achilles, rotator cuff, patella, and/or lateral epicondyle (tennis elbow). Select, recent (ie, 2019 to present) systematic reviews of RCTs and/or nonrandomized studies are described next. A crosswalk of RCTs included in these systematic reviews is found in the Appendix (Table A1). Characteristics and results of these systematic reviews are found in Tables 1 and 2.

Masiello et al (2022) conducted a systematic review and meta-analysis of 33 RCTs (N=2025) comparing ultrasound-guided platelet-rich plasma to control (injection of steroids, saline, autologous whole blood, mesenchymal stem cells, or local anesthetic; dry needling; prolotherapy; or other non-injection intervention) for the treatment of tendinopathy.[7,] Tendinopathies included lateral epicondylitis (n=8), plantar fasciitis (n=5), Achilles tendinopathy (n=5), rotator cuff tendinopathy (n=7), patellar tendinopathy (n=3), and carpal tunnel syndrome (n=3). Most trials (n=20) administered platelet-rich plasma as a single injection; however, up to 4 injections were administered in some trials. Few differences in efficacy between control and platelet-rich plasma were found with the exception of patients with carpal tunnel where pain and severity scores were reduced in the short and medium term. Results were reported for individual tendinopathies and, therefore, are not included in Table 2. However, overall mean differences in pain scores were: -0.24 (95% confidence interval [CI], -0.73 to 0.25) for lateral epicondylitis, -3.62 (95% CI, -8.16 to 0.91) for plantar fasciitis, -0.17 (95% CI, -4.25 to 3.90) for Achilles tendinopathy, 0.16 (95% CI, -0.18 to 0.50) for rotator cuff

tendinopathy, 0.17 (95% CI, -0.64 to 0.98) for patellar tendinopathy, and -0.24 (95% CI, -0.32 to -0.16) for carpal tunnel syndrome. The evidence was rated as low quality due to risk of bias, imprecision, and inconsistency.

Dai et al (2023) conducted a systematic review and meta-analysis of RCTs evaluating platelet-rich plasma versus control (saline injection, dry needling, or no treatment) for the treatment of tendinopathy.[8] A total of 13 trials met the eligibility criteria and included patients with lateral epicondylitis (5 RCTs), Achilles tendinopathy (4 RCTs), rotator cuff tendinopathy (2 RCTs), and patellar tendinopathy (2 RCTs). Among the 13 RCTs, 7 studies were judged to be at low risk of bias and 6 were found to have a high risk of bias. The meta-analysis demonstrated that platelet-rich plasma was not superior to control for the primary outcomes of change in pain intensity or function at 12 weeks; these trends also persisted at 24 weeks. The authors noted that included trials displayed significant heterogeneity with respect to platelet-rich plasma preparation and patient characteristics, and had important methodological limitations.

Muthu et al (2021) conducted a systematic review with meta-analysis of RCTs comparing platelet-rich plasma, autologous blood, corticosteroids, local anesthetics, laser therapy, and surgery for patients with lateral epicondylitis.[9] A total of 25 trials met the eligibility criteria (N=2040). Results demonstrated that based on data from 22 trials, only leukocyte-rich platelet-rich plasma significantly improved visual analog scale (VAS) pain scores compared to saline control (weighted mean difference [MD], -14.8; 95% confidence interval [CI], -23.18 to -6.39); in a subgroup analysis of 14 studies with at least 12 months of follow up, the weighted MD did not reach statistical significance (-7.69; 95% CI, -27.28 to 11.90). Based on data from 11 trials, none of the interventions were superior to saline control for improvement in the Disabilities of the Arm, Shoulder and Hand (DASH) score. Treatment ranking based on the P-score approach demonstrated that leukocyte-rich platelet-rich plasma was most likely to be the best treatment amongst autologous blood, corticosteroids, laser therapy, local anesthetics, and leukocyte-poor platelet-rich plasma.

Johal et al (2019) conducted a systematic review and meta-analysis of RCTs on platelet-rich plasma for various orthopedic indications, including 10 RCTs of lateral epicondylitis.[10] The meta-analysis evaluated the standardized mean difference in pain at both 3 and 12 months. Systematic review authors used the Cochrane Collaboration risk of bias tool to assess study quality. At 12 months, pain scores were statistically significantly lower for platelet-rich plasma versus its comparators (ie, steroids, whole blood, dry needling, local anesthetics). However, these results should be interpreted with caution due to important limitations including high statistical heterogeneity (I^2=73%), lack of a clinically significant difference (ie, < effect size threshold of 0.5 for a clinically important difference), and moderate to high risk of bias in study conduct.

Table 1. Systematic Reviews & Meta-Analysis Characteristics

Study	Dates	Trials	Participants	N (Range)	Design	Duration
Masiello (2022)[7]	Through 2021	33	Patients with tendinopathy	2025 (NR)	RCT	3 to 36 mo
Dai (2023)[8]	2010-2020	13	Patients with tendinopathy	576 (23 to 79)	RCT	4 to ≥24 wk
Muthu (2021)[9]	2010-2020	25	Patients with lateral epicondylitis	2040 (25 to 230)	RCT	3 to 24 mo

Johal (2019)[10]	2010-2016	10	Patients with lateral epicondylitis	25 - 231	RCT	6 wk to 24 mo

NR: not reported; RTC: randomized controlled trial.

Table 2. Systematic Reviews & Meta-Analysis Results

Study	SMD in Pain for PRP	SMD in functional disability for PRP	WMD in pain reduction (between LR-PRP and control)	WMD in functional disability (between LR-PRP and control)	WMD in pain reduction at 3 months (between LR-PRP and control)	WMD in pain reduction at 1 year (between LR-PRP and control)
Dai (2023)[8]	-0.14	0.18				
95% CI	-0.55 to 0.26	-0.13 to 0.49				
Muthu (2021)[9]			-14.8	-8.77		-7.69
95% CI			-23.18 to -6.39	30.60 to 13.07		-27.28 to 11.90
Johal (2019[10.	-0.69					
95% CI	-1.15 to -0.23					

CI: confidence interval; LR: leukocyte-rich; PRP: platelet-rich plasma; SMD: standard mean difference; WMD: weighted mean difference;.

Randomized Controlled Trials

One larger RCT not included in the above systematic reviews was also published in 2021 (N=240) comparing platelet-rich plasma to sham control. [11]Victorian Institute of Sport Assessment-Achilles (VISA-A) score was not significantly different between groups. Tables 3 and 4 summarize the RCT characteristics and results, respectively, and Tables 5 and 6 describe study design and conduct limitations.

Table 3. Summary of Key RCT Characteristics

Study	Countries	Sites	Dates	Participants	Interventions	Comparator	
					Active	Comparator 1	Comparator 2
Kearney (2021)[11]	UK	24	2016-2020	Adults with painful midportion Achilles tendinopathy lasting longer than 3 months	PRP (n=121)	Sham (n=119)	

RCT: randomized controlled trial; PRP: platelet-rich plasma; CS: corticosteroids; LR: leukocyte-rich; LP: leukocyte-poor; NR: Not reported; UK: United Kingdom;

Table 4. Summary of Key RCT Results

Study	VAS Score	WOMAC	Other pain / disability assessment
Kearney (2021)[11]			6 mo VISA-A score
PRP			54.4
Sham			53.4
Adjusted MD; 95% CI			-2.7 (-8.8 to 3.3)
P-value			0.0003

CI: confidence interval;MD: mean difference; PRP: platelet-rich plasma; RCT: randomized controlled trial; VISA-A: Victorian Institute of Sport Assessment-Achilles score

Table 5. Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Follow.Up[e]
Kearney (2021) [11]		1. 37 participants received additional treatments during the 6-month follow up	1. 40 participants received additional treatments during the 6-month follow up		

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Population key: 1. Intended use population unclear; 2. Study population is unclear; 3. Study population not representative of intended use; 4, Enrolled populations do not reflect relevant diversity; 5. Other.
[b] Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest (e.g., proposed as an adjunct but not tested as such); 5: Other.
[c] Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively; 5. Other.
[d] Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. Incomplete reporting of harms; 4. Not establish and validated measurements; 5. Clinically significant difference not prespecified; 6. Clinically significant difference not supported; 7. Other.
[e] Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms; 3. Other.

Table 6. Study Design and Conduct Limitations

Study	Allocation[a]	Blinding[b]	Selective Reporting[c]	Follow Up[d]	Power[e]	Statistical[f]
Kearney (2021)[11]		1. Single blinded (participants only)				

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

[a] Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias.

[b] Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician.

[c] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.

[d] Follow-Up key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials).

[e] Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference. 4. Underpowered

[f] Statistical key: 1. Intervention is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Intervention is not appropriate for multiple intervals and/or p values not reported; 4. Comparative treatment effects not calculated

Section Summary: Platelet-Rich Plasma as a Primary Treatment of Tendinopathy
Multiple RCTs and systematic reviews with meta-analyses have evaluated the efficacy of platelet-rich plasma injections in individuals who have tendinopathy. The majority of the more recently-published systematic reviews and meta-analyses that only included RCTs failed to show a statistically and/or clinically significant impact on symptoms (ie, pain) or functional outcomes. Although 1 systematic review found statistically significantly lower pain scores at 12 months with platelet-rich plasma versus the comparators, its results should be interpreted with caution due to important study conduct limitations. Additionally, in a recent RCT compared to sham control, platelet-rich plasma did not significantly improve pain after 6 or 12 months.

PLATELET-RICH PLASMA AS A PRIMARY TREATMENT OF NON-TENDON SOFT TISSUE INJURY OR INFLAMMATION

Clinical Context and Therapy Purpose
The purpose of platelet-rich plasma injections is to provide a treatment option that is an alternative to or an improvement on existing therapies, such as nonpharmacologic therapy (eg, exercise, physical therapy), analgesics, and anti-inflammatory agents, in individuals with non-tendon soft tissue injury or inflammation (eg, plantar fasciitis).

The following PICO was used to select literature to inform this review.

Populations
The relevant population of interest is individuals with non-tendon soft tissue injury or inflammation (eg, plantar fasciitis).

Interventions
The therapy being considered is platelet-rich plasma injections. The use of platelet-rich plasma has been proposed as a treatment for various musculoskeletal conditions and as an adjunctive procedure in orthopedic surgeries. The potential benefit of platelet-rich plasma has received considerable interest due to the appeal of a simple, safe, low-cost, and minimally invasive method of applying growth factors.

Comparators
Comparators of interest include nonpharmacologic therapy (eg, exercise, physical therapy), analgesics, and anti- inflammatory agents.

Outcomes
The general outcomes of interest are symptoms, functional outcomes, health status measures, quality of life, and treatment-related morbidity. The existing literature evaluating platelet-rich plasma injections as a treatment for non-tendon soft tissue injury or inflammation (eg, plantar fasciitis) has varying lengths of follow-up. While studies described below all reported at least 1 outcome of interest, longer follow-up was necessary to fully observe outcomes. Therefore, 2 years of follow-up is considered necessary to demonstrate efficacy.

Study Selection Criteria
Methodologically credible studies were selected using the principles discussed under the first indication.

REVIEW OF EVIDENCE
In individuals with non-tendon soft tissue injury or inflammation (eg, plantar fasciitis), there are no large double-blind RCT's of sufficient duration (ie, 2 years) to demonstrate efficacy.

Systematic Reviews

Seth et al (2023) published a systematic review comparing corticosteroid injections to either platelet-rich plasma or extracorporeal shock wave therapy in patients with plantar fasciitis.[12] The studies were limited to RCTs up to April 2021. A total of 18 studies were included, 12 of which evaluated platelet-rich plasma compared to corticosteroid injections. VAS scores were higher in the corticosteroid group than the platelet-rich plasma group at both 3 (MD, 0.62; 95% CI, 0.13 to 1.12; p=.01) and 6 months (MD, 1.49; 95% CI, 0.22 to 2.76; p=.02). Notably, numerical differences between groups were small. Functional outcomes were similar with corticosteroids compared to platelet-rich plasma at 3 months but worse with corticosteroids at 6 months (American Orthopaedic Foot and Ankle Society [AOFAS] MD, -11.53; 95% CI, -16.62 to -6.43; p<.0001). The authors deemed the evidence very low quality, and most studies had either high or unclear risk of bias.

Randomized Controlled Trials
There are several additional RCTs not included in the Seth et al (2023) review. [13,14,15] None were large double-blind RCT's of sufficient duration (ie, 2 years) to conclusively demonstrate efficacy. The RCTs compared platelet-rich plasma treatment with corticosteroid injection or saline injection. The platelet-rich plasma protocols differed across RCTs. The RCTs were small, ranging in size from 28[15] to 155 participants.[13] Follow-up duration ranged from 6 months[15,16] to 18 months.[14] Two were conducted in single centers in either the United Kingdom,[15] India[14], The other was a multicenter RCT of 5 sites in the Netherlands.[15] None prespecified any methods to assess potential harms. Results were mixed across RCTs. The largest RCT (N=115) by Peerbooms et al (2019) compared platelet-rich plasma with corticosteroid injection and had a follow-up to 12 months.[13] In the RCT by Peerbooms et al (2019), the proportion of patients with at least a 25% improvement in Foot Function Index Pain Scores between baseline and 12 months was significantly greater in the platelet-rich plasma group (88.4% vs. 55.6%; p=.003). Additionally, mean Foot Function Index Disability Scores

were significantly lower in the platelet-rich plasma group at 12 months (mean difference, 12.0; 95% CI, 2.3 to 21.6). But, these improvements did not translate into significantly greater quality of life in the platelet-rich plasma group. Also, important study design and conduct gaps exist that seriously limit the interpretation of these findings, including that analysis excluded 29% of the randomized patients, which was less than the calculated sample size. Therefore, although evidence continues to develop, important uncertainties in efficacy and safety remain and larger double-blind RCT's are still needed.

Section Summary: Platelet-Rich Plasma as a Primary Treatment of Non-Tendon Soft Tissue Injury or Inflammation
Several small RCTs multiple prospective observational studies and systematic reviews have evaluated the efficacy of PRP injections in individuals with chronic plantar fasciitis. The preparation of platelet-rich plasma and outcome measures differed across studies. Results among the RCTs were inconsistent. The largest of the 3 RCTs showed that treatment using platelet-rich plasma compared with corticosteroids resulted in statistically significant improvements in pain and disability, but not quality of life. Larger RCTs completed over a sufficient duration of time (ie, 2 years) are still needed to address important uncertainties in efficacy and safety.

PLATELET-RICH PLASMA AS A PRIMARY TREATMENT OF OSTEOCHONDRAL LESIONS

Clinical Context and Therapy Purpose
The purpose of platelet-rich plasma injections is to provide a treatment option that is an alternative to or an improvement on existing therapies, such as nonpharmacologic therapy (eg, exercise, physical therapy), analgesics, anti-inflammatory agents, and surgery in individuals with osteochondral lesions.

The following PICO was used to select literature to inform this review.

Populations
The relevant population of interest is individuals with osteochondral lesions.

Interventions
The therapy being considered is platelet-rich plasma injections. The use of platelet-rich plasma has been proposed as a treatment for various musculoskeletal conditions and as an adjunctive procedure in orthopedic surgeries. The potential benefit of platelet-rich plasma has received considerable interest due to the appeal of a simple, safe, low-cost, and minimally invasive method of applying growth factors.

Comparators
Comparators of interest include nonpharmacologic therapy (eg, exercise, physical therapy), analgesics, anti-inflammatory agents, and surgery.

Outcomes
The general outcomes of interest are symptoms, functional outcomes, health status measures, quality of life, and treatment-related morbidity. The existing literature evaluating platelet-rich

plasma injections as a treatment for osteochondral lesions has varying lengths of follow-up. While studies described below all reported at least one outcome of interest, longer follow-up was necessary to fully observe outcomes. Therefore, 28 weeks of follow-up is considered necessary to demonstrate efficacy.

Study Selection Criteria

Methodologically credible studies were selected using the principles discussed under the first indication.

REVIEW OF EVIDENCE

Comparative Studies

No high-quality RCTs on treatment of osteochondral lesions were identified. Mei-Dan et al (2012) reported a quasi-randomized study of 29 patients with 30 osteochondral lesions of the talus assigned to 3 intra-articular injections of hyaluronic acid or platelet-rich plasma.[17] At 28-week follow-up, scores on the AOFAS Ankle-Hindfoot Scale improved to a greater extent in the platelet-rich plasma group (from 68 to 92) than in the hyaluronic acid group (from 66 to 78) ($p<.05$). Subjective global function also improved to a greater extent in the platelet-rich plasma group (from 58 to 91) than in the hyaluronic acid group (from 56 to 73). Interpretation of the composite measures of visual analog scale scores for pain and function is limited by differences between the groups at baseline. Also, neither the patients nor the evaluators were blinded to treatment in this small study.

Section Summary: Platelet-Rich Plasma as a Primary Treatment of Osteochondral Lesions

A single quasi-randomized study evaluated the efficacy of platelet-rich plasma injections in individuals who have osteochondral lesions. Compared with hyaluronic acid, treatment with platelet-rich plasma resulted in statistically significant improvements in AOFAS Ankle-Hindfoot Scale scores and global function, indicating improved outcomes. Adequately powered and blinded RCTs are required to confirm these findings.

PLATELET-RICH PLASMA AS A PRIMARY TREATMENT OF KNEE OR HIP OSTEOARTHRITIS

Clinical Context and Therapy Purpose

The purpose of platelet-rich plasma injections is to provide a treatment option that is an alternative to or an improvement on existing therapies, such as nonpharmacologic therapy (eg, exercise, physical therapy), analgesics, anti-inflammatory agents, and surgery, in individuals with knee or hip osteoarthritis.

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is individuals with knee or hip osteoarthritis.

Interventions
The therapy being considered is platelet-rich plasma injections. The use of platelet-rich plasma has been proposed as a treatment for various musculoskeletal conditions and as an adjunctive procedure in orthopedic surgeries. The potential benefit of platelet-rich plasma has received considerable interest due to the appeal of a simple, safe, low-cost, and minimally invasive method of applying growth factors.

Comparators
Comparators of interest include nonpharmacologic therapy (eg, exercise, physical therapy), analgesics, anti-inflammatory agents, and surgery.

Outcomes
The general outcomes of interest are symptoms, functional outcomes, health status measures, quality of life, and treatment-related morbidity. The existing literature evaluating platelet-rich plasma injections as a treatment for knee or hip osteoarthritis has varying lengths of follow-up, ranging from 6 to 12 months. While studies described below all reported at least 1 outcome of interest, longer follow-up was necessary to fully observe outcomes. Therefore, 12 months of follow-up is considered necessary to demonstrate efficacy.

Study Selection Criteria
Methodologically credible studies were selected using the principles described in the first indication

REVIEW OF EVIDENCE
A number of RCTs and several systematic reviews of RCTs evaluating use of PRP for knee osteoarthritis have been published.[10,18,19,20,21,22,23,24,25,26] Protocols used in platelet-rich plasma interventions for knee osteoarthritis varied widely. For example, in the studies identified in the Laudy et al (2015) systematic review, platelet-rich plasma was prepared using single, double, or triple spinning techniques, and interventions included between 1 and 3 injections delivered 1 to 3 weeks apart.[20]

Systematic Reviews
In individuals with knee osteoarthritis undergoing platelet-rich plasma injections, findings from 6 systematic reviews are reported.[10,18,19,20,21,27] The systematic reviews have varied in their outcomes of interest and their findings. Systematic reviews have generally found that platelet-rich plasma was more effective than placebo or hyaluronic acid in reducing pain and improving function. However, systematic review authors have noted that their findings should be interpreted with caution due to important limitations including significant residual statistical heterogeneity, questionable clinical significance, and high risk of bias in study conduct.

Anil et al (2021) published a systematic review with network meta-analysis to compare the efficacy of nonoperative injectable treatments for knee osteoarthritis (Tables 7 and 8).[18] A total of 79 RCTs (N=8761) were included and the follow-up ranged from 4 weeks to 24 months. Intra-articular injectable treatments included platelet-rich plasma, autologous conditioned serum, bone marrow aspirate concentrate, botulinum toxin, corticosteroids, hyaluronic acid, mesenchymal stem cells, ozone, saline placebo, plasma rich in growth factor, and stromal vascular fraction; the publication did not delineate the number of RCTs that specifically evaluated on platelet-rich plasma. At 12 months, the treatment with the highest P-Score for the

MD in Western Ontario and McMaster Osteoarthritis Index (WOMAC) scale score and VAS score was stromal vascular fraction. However, the MD in WOMAC scale and VAS scores for leukocyte-poor platelet-rich plasma and leukocyte-rich platelet-rich plasma versus saline placebo at 12 months did not reach statistical significance.

Trams et al (2020) published a systematic review that included 38 RCTs (N = 2962) evaluating the effects of platelet-rich plasma (PRP) on patients with knee osteoarthritis (Tables 7 and 8).[19] The meta-analysis focused on the review of 33 blinded studies. Follow-up ranged from 6 months to 2 years. Comparators included hyaluronic acid in 23 studies, placebo (eg, saline, no injection, physical therapy) in 10 studies, corticosteroids in 4 studies, and acetaminophen in 2 studies. Twenty-two studies reported visual analog scale (VAS) pain outcomes for placebo (n = 5), hyaluronic acid (n = 15), and corticosteroids (n = 2). Placebo and hyaluronic acid subgroups showed significant VAS differences in favor of platelet-rich plasma (p<.00001). The corticosteroid subgroup was not significantly different from platelet-rich plasma (p=.23). Six studies comparing single versus multiple injections of platelet-rich plasma showed a significant difference in favor of 3 platelet-rich plasma injections (p<.00001). Functional outcomes were reported via the WOMAC scale for placebo (n=9), corticosteroids (n=1), and hyaluronic acid (n=15). Both pooled and subgroup analyses favored platelet-rich plasma (p<.00001). In 5 studies assessing multiple versus single platelet-rich plasma injections, significant differences in favor of multiple injections were found (p<.00001). Functional outcomes assessed via International Knee Documentation Committee (IKDC) scores were reported in 2 placebo studies and 5 hyaluronic acid studies. While a significant difference was found for hyaluronic acid (p=.004), no significant difference was found for placebo (p=.24). Pooled estimates for 6 studies comparing platelet-rich plasma to corticosteroids, hyaluronic acid, or mesenchymal stem cells found no significant differences in Knee injury and Osteoarthritis Outcome Score (KOOS) sport, quality of life, activities of daily living, symptoms, or pain subscales. The pooled estimates for adverse events showed non-significant differences in favor of the control groups (p=.15). The risk of bias was assessed using Cochrane criteria. One study was at high risk of bias for 3 domains, 2 studies were at high risk of bias for 2 domains, and 12 studies were at high risk of bias for 1 domain. The most impacted domains were performance bias and reporting bias.

Johal et al (2019) conducted a systematic review and meta-analysis of RCTs comparing platelet-rich plasma with hyaluronic acid (8 trials, n=927), placebo (2 trials, n=105), no platelet-rich plasma (2 trials, n=123) acetaminophen (1 trial, n=75), or a corticosteroid (1 trial, n=48).[10] Meta-analysis of VAS pain scores showed that platelet-rich plasma was more effective than its comparators at 12 months (standard mean difference, -0.91; 95% CI, -1.41 to -0.41). However, the systematic review authors noted that important limitations of this finding included lack of a clinically significant difference (i.e., less than the effect size threshold of 0.5 for a clinically important difference), high residual statistical heterogeneity between studies (I^2=89%), and high risk of bias in study conduct.

Xu et al (2017) conducted a systematic review and meta-analysis of RCTs comparing platelet-rich plasma with hyaluronic acid (8 trials), or placebo (2 trials), for the treatment of knee osteoarthritis (Tables 7 and 8).[27] Risk of bias was assessed using Cochrane criteria. Four studies were assessed as being of low quality, 3 as moderate quality, and 3 as high quality. Meta-analyses including 7 of the trials comparing platelet-rich plasma with hyaluronic acid showed that platelet-rich plasma significantly improved the WOMAC or IKDC scores compared

with hyaluronic acid at 6-month follow-up; however, when meta-analyses included only the 2 high-quality RCTs, there was not a significant difference between platelet-rich plasma and hyaluronic acid (Table 8). Also note that the WOMAC evaluates 3 domains: pain, scored from 0 to 20; stiffness, scored from 0 to 8; and physical function, scored from 0 to 68. Higher scores represent greater pain and stiffness as well as worsened physical capability. The IKDC is a patient-reported, knee-specific outcome measure that measures pain and functional activity. In the meta-analysis comparing platelet-rich plasma with placebo, a third trial was included, which had 4 treatment groups, 2 of which were platelet-rich plasma and placebo. This analysis showed that platelet-rich plasma significantly improved WOMAC or IKDC scores compared with placebo; however, only 1 of the trials was considered high quality and that trial only enrolled 30 patients. All meta-analyses showed high heterogeneity among trials (I^2≥90%).

Laudy et al (2015) conducted a systematic review of RCTs and nonrandomized clinical trials to evaluate the effect of platelet-rich plasma on patients with knee osteoarthritis (Tables 7 and 8).[20] Ten trials (N=1110) were selected. Cochrane criteria for risk of bias were used to assess study quality, with 1 trial rated as having a moderate risk of bias and the remaining 9 trials as high risk of bias. While meta-analyses showed that platelet-rich plasma was more effective than placebo or hyaluronic acid in reducing pain and improving function (Table 8), larger randomized studies with lower risk of bias are needed to confirm these results.

Chang et al (2014) published a systematic review that included 5 RCTs, 3 quasi-randomized controlled studies, and 8 single-arm prospective series (N=1543) (Tables 7 and 8).[21] The Jadad scale was used to assess RCTs, and the Newcastle-Ottawa Scale was used to assess the other studies; however, results of the quality assessments were not reported. Meta-analysis of functional outcomes at 6 months found that the effectiveness of platelet-rich plasma (effect size, 1.5; 95% CI, 1.0 to 2.1) was greater than that of hyaluronic acid (effect size, 0.7; 95% CI, 0.6 to 0.9; when only RCTs were included). However, there was no significant difference at 12-month follow-up between platelet-rich plasma (effect size, 0.9; 95% CI, 0.5 to 1.3) and hyaluronic acid (effect size, 0.9; 95% CI, 0.5 to 1.2; when only RCTs were included). Fewer than 3 injections, single spinning, and lack of additional activators led to greater uncertainty in the treatment effects. Platelet-rich plasma also had lower efficacy in patients with higher degrees of cartilage degeneration. Results were consistent when analyzing only RCTs, but asymmetry in funnel plots suggested significant publication bias.

Table 7. Systematic Review Characteristics for Knee or Hip Osteoarthritis

Study	Search Date	Trials	Participants	Design
Anil et al (2021)[18]	Through 2020	RCTs of patients receiving PRP, autologous conditioned serum, bone marrow aspirate concentrate, botulinum toxin, corticosteroids, hyaluronic acid, mesenchymal stem cells, ozone, saline placebo, plasma rich in growth factor, or stromal vascular fraction	Patients with knee OA	79 RCTs
Trams et al (2020)[19]	2005-2020	· 10 PRP vs placebo · 23 PRP vs HA · 4 PRP vs corticosteroid · 2 PRP vs acetaminophen · 6 PRP, single vs multiple injections		· 38 RCTs

Johal et al (2019)[10]	Through Feb 2017	· 8 PRP vs HA · 2 PRP vs placebo · 2 PRP vs no PRP · 1 PRP vs corticosteroid · 1 PRP vs acetaminophen	Patients with knee OA	· 14 RCTs
Xu et al (2017)[27]	Through May 2016	· 8 PRP vs HA · 2 PRP vs placebo	Patients with knee OA	· 10 RCTs
Laudy et al (2015)[20]	Through Jun 2014	· 8 PRP vs HA · 1 PRP vs placebo · 1 PRP, different preparations	Patients with knee OA	· 6 RCTs · 4 nonrandomized
Chang et al (2014)[21]	Through Sep 2013	· 6 PRP vs HA · 1 PRP vs placebo · 1 PRP, different preparations · 8 single-arm PRP	Patients with knee OA	· 5 RCTs · 3 quasi-randomized · 8 single-arm

HA: hyaluronic acid; OA: osteoarthritis; PRP: platelet-rich plasma; RCT: randomized controlled trial.

Table 8. Systematic Review Functional Score Results for Knee or Hip Osteoarthritis

Study	Change in Functional Scores (95% CI)[a]	
	6 Months – 2 Years	
Anil et al (2021)[18]	WOMAC at 1 year: Leukocyte-poor PRP vs saline placebo, -7.65 (-27.18 to 11.88); Leukocyte-rich PRP vs saline placebo, -13.28 (-28.74 to 2.18)	
Trams et al (2020)[19]	WOMAC: All trials, -12.10 (-14.12 to -7.24); PRP vs placebo, -14.56 (-21.17 to -7. 96); PRP vs steroid, -16.10 (-19.61 to -12.59); PRP vs HA, -10,68 (-14.12 to -7.24) IKDC: All trials, 6.94 (2.53 to 11.34); PRP vs placebo, 8.96 (-5.88 to 23.81); PRP vs HA, 6.58 (2.12 to 11.05) KOOS - ADL: All trials, 1.23 (-4.85 to 7.31)	
	6 Months	12 Months
Xu et al (2017)[27]	PRP vs HA: · All trials: -0.9 (-1.4 to -0.3) · Low quality: -13.3 (-33.9 to 3.7) · Moderate quality: -1.3 (-1.6 to -1.0) · High quality: -0.1 (-0.3 to 0.1) PRP vs placebo: · All trials (3): -2.1 (-3.3 to -1.0)	NR
Laudy et al (2015)[20]	PRP vs HA: -0.8 (-1.0 to -0.6)	PRP vs HA: -1.3 (-1.8 to -0.9)
Chang et al (2014)[21]	PRP, baseline vs post-treatment: · All studies: 2.5 (1.9 to 3.1) · Single-arm: 3.1 (2.0 to 4.1) · Quasi-randomized: 3.1 (1.4 to 3.8) · RCT: 1.5 (1.0 to 2.1)	PRP, baseline vs posttreatment: · All studies: 2.9 (1.0 to 4.8) · Single-arm: 2.6 (-0.4 to 5.7) · Quasi-randomized: 4.5 (4.1 to 5.0) · RCT: 0.9 (0.5 to 1.3)

ADL: activities of daily living; CI: confidence interval; CS: corticosteroid; HA: hyaluronic acid; IKDCL International Knee Documentation Committee; KOOS: Knee Injury and Osteoarthritic Outcome Score; NR: not reported; PRP: platelet-rich plasma; RCT: randomized controlled trial; OA: osteoarthritis; WOMAC: Western Ontario McMaster Osteoarthritis Index.
a Functional outcomes were measured by the .

In individuals with hip osteoarthritis undergoing platelet-rich plasma injections, findings from 2 systematic reviews are reported. Belk et al (2022) identified 6 RCTs comparing the efficacy of platelet-rich plasma (n=211) and hyaluronic acid injections (n=197).[28] The mean follow-up was approximately 12 months. In an analysis of 4 RCTs, platelet-rich plasma and hyaluronic acid groups had similar improvements in VAS score (MD, 5.9; 95% CI, -0.741 to 1.92) and WOMAC score (MD, 0.27; 95% CI, -0.05 to 0.59). Gazendam et al (2020) identified 11 RCTs (N=1353) assessing the efficacy of platelet-rich plasma, corticosteroids, and saline injections.[29] Pooled pain and functional outcomes were reported for 2 to 4 and 6 months follow-up. No intervention significantly outperformed saline intra-articular injection at any time point. Clinically significant improvements in pain from baseline were observed for all treatment groups, including placebo.

Randomized Controlled Trials

In individuals with knee osteoarthritis undergoing platelet-rich plasma injections, RCTs with a follow-up of at least 12 months have been published subsequent to several of the above-described systematic reviews (Tables 9 to 12).[30,31,32] All trials were conducted outside of the United States. Sample sizes ranged from 40 to 200 patients. Comparator treatments included corticosteroids, celecoxib or hyaluronic acid. Two RCTs found statistically significantly greater 1-year reductions in pain and function scores with platelet-rich plasma corticosteroids or celecoxib. Sdeek et al (2021) reported on the results of a 36-month RCT that compared 3 intraarticular injections of either platelet-rich plasma (n=95) or hyaluronic acid (n=94) in patients with knee osteoarthritis.[30] Both platelet-rich plasma and hyaluronic acid were effective in improving pain and functional status. Statistical analyses were not performed, however, trends for pain and function scores showed greater improvement in the group that received platelet-rich plasma. The findings of these RCTs should be interpreted with caution due to important study conduct limitations, including potential inadequate control for selection bias and limited or unclear blinding. No significant differences in pain or function scores were observed within the first month of treatment in either study.

Dallari et al (2016) reported on results of an RCT that compared platelet-rich plasma with hyaluronic acid alone or with a combination platelet-rich plasma plus hyaluronic acid in 111 patients with hip osteoarthritis.[33] Although this well-conducted RCT reported positive results, with statistically significant reductions in VAS scores (lower scores imply less pain) at 6 months in the platelet-rich plasma arm (21; 95% CI, 15 to 28) versus the hyaluronic acid arm (35; 95% CI, 26 to 45) or the platelet-rich plasma plus hyaluronic acid arm (44; 95% CI, 36 to 52), the impact of treatment on other secondary outcome measures such as Harris Hip Score and WOMAC scores was not observed. Notably, there was no control for type I error for multiple group comparisons at different time points, and the trial design did not incorporate a sham-control arm. Nouri et al (2022) also conducted an RCT comparing platelet-rich plasma with hyaluronic acid in patients with hip osteoarthritis.[34] A total of 105 patients were randomized to platelet-rich plasma, hyaluronic acid, or the combination. There were no differences in VAS scores between groups at 6 months; however, functional outcomes were improved in the platelet-rich plasma groups compared with hyaluronic acid alone.

Table 9. Summary of Key RCT Characteristics

Study	Countries	Sites	Dates	Participants	Interventions	Comparator	
					Active	**Comparator 1**	**Comparator 2**
Nouri et al (2022) [34]	Iran	1	2019-2020	Patients with hip OA, grade II to III	**PRP (n=35); 2 x 5 mL 14 days apart**	**HA (n=35); 2 x 2.5 mL 14 days apart**	**HA + PRP (n=35); 2 x 5 mL PRP + 2.5 mL HA 14 days apart**
Sdeek et al (2021)[30]	Egypt	NR	2016-2020	Patients with knee OA, grade II to III	PRP (n=95); 3 X 2.5 mL 14 days apart	HA (n=94); 3 x 2.5 mL 14 days apart	

Reyes-Sosa et al (2020)[31]	Mexico	1	NR	Patients with knee OA, grade II-III, who were previously treated with acetaminophen without improvement	Activated PRP (n=30); 2 x 3 mL 15 days apart	NSAID: (n=30); 200 mg celecoxib every 24 hours for 1 year	
Elksnins-Finogejevs et al (2020)[32]	Latvia	1	2016 - 2017	Patients with knee OA, grade II to III	PRP (n=20); 8 ml single-dose	CS (n=20); 1 mL 40 mg/mL triamcinolone + 5 mL 2% lidocaine	
Dallari et al (2016)[33]	Italy	NR	2010 - 2011	Patients with hip OA	PRP (n=44)	PRP+HA (n=31)	HA (n=36)

CS: corticosteroid; HA: hyaluronic acid; NR: not reported; NSAID: non-steroidal anti-inflammatory drug; OA: osteoarthritis; PRP: platelet-rich plasma; RCT: randomized controlled trial.

Table 10. Summary of Key RCT Results

Study	Pain Outcomes	Functional Outcomes
Knee OA		
Sdeek et al (2021)[30]	Mean VAS Score	Mean IKDC and WOMAC Scores
PRP	Baseline: 57.8 12 months: 47.1 36 months: 40.9	IKDC: Baseline: 49.1 12 months: 67.9 36 months: 55.2 WOMAC: Baseline: 66.5 12 months: 52.8 36 months: 60.6
HA	Baseline: 59.3 12 months: 50.3 36 months: 60.3	IKDC: Baseline: 47.3 12 months: 61.6 36 months: 46.1 WOMAC: Baseline: 66.9 12 months: 54.9 36 months: 64.2
Reyes-Sosa et al (2020)[31]	Change in VAS Score from Baseline at 12 mo, %	Change in WOMAC Score from Baseline at 12 mo
PRP	-68.69 (p<.001)	-11.5[a]
Celecoxib	-40.94 (p<.001)	-4[a]
P-value for Difference	*p*<.001	*p*<.001
Elksnins-Finogejevs et al (2020)[32]	Mean VAS Score, 95% CI	Mean IKDC Score, 95% CI
PRP	Baseline: 6.1 (5.4 to 6.6) 30 weeks: 1.6 (0.7 to 2.6) 58 weeks: 2.9 (2.2 to 3.6)	Baseline: 36.3 (31.2 to 41.4) 30 weeks: 77.5 (70.6 to 84.3) 58 weeks: 62.0 (54.5 to 69.6)

CS	Baseline: 6.0 (5.2 to 6.8) 30 weeks: 4.0 (3.2 to 4.8) 58 weeks: 5.1 (4.1 to 6.0)	Baseline: 28.0 (24.6 to 33.1) 30 weeks: 56.3 (47.4 to 65.3) 58 weeks: 39.8 (32.8 to 46.8)
Hip OA		
Nouri et al (2022) [34]	VAS at 6 mo	WOMAC at 6 mo
PRP	3.13 ± 1.29	21.53 ± 10.40
HA	3.90 ± 1.40	27.21 ± 9.25
PRP + HA	3.13 ± 1.18	21.16 ± 8.00
Dallari et al (2016)[35]	VAS Score at 6 mo	NR
PRP	21	
HA	35	
PRP + HA	44	

CI: confidence interval; CS: corticosteroids; HA: hyaluronic acid; IKDC: International Knee Documentation Score; NR: not reported; OA: osteoarthritis; PCP: platelet-rich plasma; VAS: visual analog scale; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index.
a Calculated estimate.

Table 11. Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Follow-Up[e]
Nouri et al (2022),[34]					
Sdeek et al (2021) [30]					
Reyes-Sosa (2020)[31]			4. Unclear adherence to treatment.	5. Clinically significant difference not defined.	
Elksnins-Finogejevs (2020)[32]					
Dallari (2016)[33]					

The study limitations stated in this table are those notable in the current review; this is not a comprehensive limitations assessment.

[a] Population key: 1. Intended use population unclear; 2. Study population is unclear; 3. Study population not representative of intended use; 4, Enrolled populations do not reflect relevant diversity; 5. Other.
[b] Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest (e.g., proposed as an adjunct but not tested as such); 5: Other.
[c] Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively; 5. Other.
[d] Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. Incomplete reporting of harms; 4. Not establish and validated measurements; 5. Clinically significant difference not prespecified; 6. Clinically significant difference not supported; 7. Other.
[e] Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms; 3. Other.

Table 12. Study Design and Conduct Limitations

Study	Allocation[a]	Blinding[b]	Selective Reporting[c]	Follow Up[d]	Power[e]	Statistical[f]
Nouri et al (2022)[34.]		1. Patients not fully blind due to differences in administration procedures				
Sdeek et al (2021) [30]					1. Power calculations not reported; 2. Power not calculated for primary outcome	
Reyes-Sosa (2020)[31]	2. Allocation not concealed from patients or health care providers. 4. Inadequate control for selection bias in celecoxib group.	1-3. Blinding of outcome assessors not clear.	1. Not registered.		1. Power not calculated.	2. Confidence intervals not reported.
Elksnins-Finogejevs (2020)[32]	2. Allocation not concealed from patients or health care providers.	1-3. Not double-blinded.				
Dallari (2016)[33]	2. Allocation not concealed from patients or health care providers	1. Only data collectors and outcome assessors blinded to treatment assignment				

The study limitations stated in this table are those notable in the current review; this is not a comprehensive limitations assessment.
a Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias.
b Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician.
c Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.
d Follow-Up key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials).
e Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.
f Statistical key: 1. Intervention is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Intervention is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated.

Section Summary: Platelet-Rich Plasma as a Primary Treatment of Knee or Hip Osteoarthritis

Multiple RCTs and systematic reviews with meta-analysis have evaluated the efficacy of platelet-rich plasma injections in individuals with knee or hip osteoarthritis. Most trials have compared platelet-rich plasma with hyaluronic acid for knee osteoarthritis. A single RCT compared platelet-rich plasma with hyaluronic acid alone or combination platelet-rich plasma plus hyaluronic acid in hip osteoarthritis. Systematic reviews have generally found that platelet-rich plasma was more effective than placebo or hyaluronic acid in reducing pain and improving function. However, systematic review authors have noted that their findings should be

interpreted with caution due to important limitations including significant residual statistical heterogeneity, questionable clinical significance, and high risk of bias in study conduct. RCTs with follow-up durations of at least 12 months published subsequent to the systematic reviews found statistically significantly greater 12-month reductions in pain and function outcomes, but these findings were also limited by important study conduct flaws including potential inadequate control for selection bias and limited or unclear blinding. Also, benefits were not maintained at 5 years. Using hyaluronic acid as a comparator is questionable because the evidence demonstrating the benefit of hyaluronic acid treatment for osteoarthritis is not robust. Two systematic reviews evaluating hip osteoarthritis did not report any statistically or clinically significant differences in pain or functional outcomes compared to hyaluronic acid, corticosteroids, or placebo. Additional larger controlled studies comparing platelet-rich plasma with placebo and alternatives other than hyaluronic acid are needed to determine the efficacy of platelet-rich plasma for knee and hip osteoarthritis. Further studies are also needed to determine the optimal protocol for delivering platelet-rich plasma.

PLATELET-RICH PLASMA AS AN ADJUNCT TO SURGERY

Anterior Cruciate Ligament Reconstruction

Clinical Context and Therapy Purpose
The purpose of platelet-rich plasma injections plus orthopedic surgery is to provide a treatment option that is an alternative to or an improvement on existing therapies, such as orthopedic surgery alone, in individuals with anterior cruciate ligament (ACL) reconstruction.

The following PICO was used to select literature to inform this review.

Populations
The relevant population of interest is individuals with ACL reconstruction.

Interventions
The therapy being considered is platelet-rich plasma injections plus orthopedic surgery. The use of platelet-rich plasma has been proposed as a treatment for various musculoskeletal conditions and as an adjunctive procedure in orthopedic surgeries. The potential benefit of platelet-rich plasma has received considerable interest due to the appeal of a simple, safe, low-cost, and minimally invasive method of applying growth factors.

Comparators
Comparators of interest include orthopedic surgery alone.

Outcomes
The general outcomes of interest are symptoms, functional outcomes, health status measures, quality of life, morbid events, resource utilization, and treatment-related morbidity. The existing literature evaluating platelet-rich plasma injections plus orthopedic surgery as a treatment for ACL reconstruction has varying lengths of follow-up. While studies described below all reported at least 1 outcome of interest, longer follow-up was necessary to fully observe outcomes. Therefore, 2 years of follow-up is considered necessary to demonstrate efficacy.

Study Selection Criteria
Methodologically credible studies were selected using the principles discussed under the first indication.

REVIEW OF EVIDENCE

Systematic Reviews

A Cochrane review by Moraes et al (2014) on platelet-rich therapies for musculoskeletal soft tissue injuries identified 2 RCTs and 2 quasi-randomized studies (N=203) specifically on platelet-rich plasma used in conjunction with ACL reconstruction.[36] Pooled data found no significant difference in IKDC scores between the platelet-rich plasma and control groups.

A systematic review and meta-analysis by Trams et al (2020) identified 16 RCTs (N=740).[19] Five studies showed no significant overall difference with respect to pain (p=.43). In 4 studies reporting IKDC scores, no significant differences were noted (p=.83). In 4 studies, no significant differences in functional outcomes as measured by the Lysholm score were reported (p=.19). Pooled estimates for Tegner scale activity assessments in 5 studies showed no significant differences (p =.38) in favor of the control. Twelve studies were deemed to be at high risk of bias in at least 1 domain.

A systematic review and meta-analysis by Lv et al (2022) identified 17 RCTs (N=970) in patients undergoing ACL reconstruction.[37] Compared to controls, platelet-rich plasma improved VAS score (MD, -1.12; 95% CI, -1.92 to -0.31; p=.007), Lysholm score (MD, 8.49; 95%CI, 1.63 to 15.36) and subjective IKDC score (MD, 6.08; 95% CI, 4.39 to 7.77; p<.00001) at 6 months. The authors only considered the difference in pain score to be clinically relevant, and they did not consider any differences between groups at 12 months to be clinically meaningful (VAS MD, -0.47 and subjective IKDC score MD, 3.99). Overall, the evidence was determined to be of moderate quality.

Randomized Controlled Trials
One of the largest RCTs, reported by Nin et al (2009), randomized 100 patients to arthroscopic ACL reconstruction with or without platelet-rich plasma.[38] The use of platelet-rich plasma on the graft and inside the tibial tunnel in patients treated with bone-patellar tendon-bone allografts had no discernible clinical or biomechanical effect at 2-year follow-up.

Retrospective Cohort Studies
Bailey et al (2021) reported on a retrospective matched case-control study evaluating the effects of intraoperative platelet-rich plasma on postoperative knee function and complications at 2 years after ACL reconstruction with meniscal repair.[39] The study was conducted between 2013 and 2017 and included 162 patients who received platelet-rich plasma and 162 patients who did not. Results demonstrated that there were no differences in knee function scores between the platelet-rich plasma and matched-control groups at 2 years, as well as no differences in the timing of return to activity (mean, 7.8 vs 8.0 months; p=.765). However, the platelet-rich plasma group demonstrated a higher rate of postoperative knee motion loss compared with the control group (13.6% vs 4.6%; p<.001).

Subsection Summary: Platelet-Rich Plasma as Adjunctive Treatment of Anterior Cruciate Ligament Reconstruction

Several systematic reviews that included multiple RCTs, quasi-randomized studies, and/or prospective studies have evaluated the efficacy of platelet-rich plasma injections in individuals undergoing ACL reconstruction. Three systematic reviews conducted a meta-analysis, Two showed that adjunctive platelet-rich plasma treatment did not result in a significant effect on function and activity outcomes, including IKDC score. One systematic review did find statistically significant benefit with platelet-rich plasma compared with control in terms of VAS, Lysholm score, and IKDC at 6 months; however, the authors only considered the differences in pain scores to be clinically relevant. By 12 months, none of the differences between groups were clinically relevant. Individual studies have shown mixed results. A retrospective matched case-control study found no differences in knee function scores or time to return of activity between platelet-rich plasma and matched-control groups at 2 years; however, the platelet-rich plasma group demonstrated a higher rate of postoperative knee motion loss compared with the control group (13.6% vs 4.6%).

Hip Fracture

Clinical Context and Therapy Purpose

The purpose of platelet-rich plasma injections plus orthopedic surgery is to provide a treatment option that is an alternative to or an improvement on existing therapies, such as orthopedic surgery alone, in individuals with hip fracture.

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is individuals with hip fracture.

Interventions

The therapy being considered is platelet-rich plasma injections plus orthopedic surgery. The use of platelet-rich plasma has been proposed as a treatment for various musculoskeletal conditions and as an adjunctive procedure in orthopedic surgeries. The potential benefit of platelet-rich plasma has received considerable interest due to the appeal of a simple, safe, low-cost, and minimally invasive method of applying growth factors.

Comparators

Comparators of interest include orthopedic surgery alone.

Outcomes

The general outcomes of interest are symptoms, functional outcomes, health status measures, quality of life, morbid events, resource utilization, and treatment-related morbidity. The existing literature evaluating platelet-rich plasma injections plus orthopedic surgery as a treatment for hip fracture has varying lengths of follow-up. While studies described below all reported at least 1 outcome of interest, longer follow-up was necessary to fully observe outcomes.

Study Selection Criteria

Methodologically credible studies were selected using the principles described in the first indication.

REVIEW OF EVIDENCE

Randomized Controlled Trials

One RCT was identified for the treatment of hip fracture with platelet-rich plasma. Griffin et al (2013) reported a single-blind randomized trial assessing the use of PRP platelet-rich plasma for the treatment of hip fractures in patients ages 65 years and older.[40] Patients underwent internal fixation of a hip fracture with cannulated screws and were randomized to standard-of-care fixation (n=99) or standard-of-care fixation plus injection of PRP into the fracture site (n=101). The primary outcome measure was the failure of fixation within 12 months, defined as any revision surgery. The overall risk of revision by 12 months was 36.9%, and the risk of death was 21.5%. There was no significant risk reduction (39.7% control versus 34.1% PRP; absolute risk reduction, 5.6%; 95% CI, -10.6% to 21.8%) or significant difference between groups for most of the secondary outcome measures. For example, mortality was 23% in the control group and 20% in the platelet-rich plasma group. The length of stay was significantly reduced in the platelet-rich plasma treated group (median difference, 8 days). For this measure, there is a potential for bias from the nonblinded treating physician.

Subsection Summary: Platelet-Rich Plasma as Adjunctive Treatment for Hip Fracture
A single open-label RCT has evaluated the efficacy of platelet-rich plasma injections in individuals with a hip fracture. This trial failed to show any statistically significant reductions in the need for revision surgery after platelet-rich plasma treatment.

Long-Bone Nonunion

Clinical Context and Therapy Purpose
The purpose of platelet-rich plasma injections plus orthopedic surgery is to provide a treatment option that is an alternative to or an improvement on existing therapies, such as Recombinant human bone morphogenetic protein-7 (rhBMP-7) plus orthopedic surgery, in individuals with long bone nonunion.

The following PICO was used to select literature to inform this review.

Populations
The relevant population of interest is individuals with long bone nonunion.

Interventions
The therapy being considered is platelet-rich plasma injections plus orthopedic surgery. The use of platelet-rich plasma has been proposed as a treatment for various musculoskeletal conditions and as an adjunctive procedure in orthopedic surgeries. The potential benefit of platelet-rich plasma has received considerable interest due to the appeal of a simple, safe, low-cost, and minimally invasive method of applying growth factors.

Comparators
Comparators of interest include rhBMP-7 plus orthopedic surgery.

Outcomes

The general outcomes of interest are symptoms, functional outcomes, health status measures, quality of life, morbid events, resource utilization, and treatment-related morbidity. The existing literature evaluating platelet-rich plasma injections plus orthopedic surgery as a treatment for long bone nonunion has varying lengths of follow-up. While studies described below all reported at least 1 outcome of interest, longer follow-up was necessary to fully observe outcomes.

Study Selection Criteria

Methodologically credible studies were selected using the principles described in the first indication.

REVIEW OF EVIDENCE

Systematic Reviews

A Cochrane review by Griffin et al (2012) found only 1 small RCT (N=21) evaluating platelet-rich plasma for long-bone healing.[41] However, because only studies comparing platelet-rich plasma with no additional treatment or a placebo were eligible for inclusion, reviewers did not select a larger RCT by Calori et al (2008; discussed below).[42]

Randomized Controlled Trials

The trial study by Dallari et al (2007), which was included in the Cochrane review, compared platelet-rich plasma plus allogenic bone graft with allogenic bone graft alone in patients undergoing corrective osteotomy for medial compartment osteoarthrosis of the knee.[35] According to Cochrane reviewers, the risk of bias in this study was substantial. Results showed no significant differences in patient-reported or clinician-assessed functional outcome scores between groups at 1 year. However, the proportion of bones united at 1 year was statistically significantly higher in the PRP plus allogenic bone graft arm (8/9) compared with the allogenic bone graft alone arm (3/9; relative risk, 2.67; 95% CI, 1.03 to 6.91). This benefit, however, was not statistically significant when assuming poor outcomes for participants who were lost to follow-up (8/11 versus 3/10; relative risk, 2.42; 95% CI, 0.88 to 6.68).

Calori et al (2008) compared the application of platelet-rich plasma with rhBMP-7 for the treatment of long-bone nonunions in an RCT involving 120 patients and 10 surgeons.[42] Inclusion criteria were posttraumatic atrophic nonunion for at least 9 months, with no signs of healing over the last 3 months, and considered as treatable only by means of fixation revision. Autologous bone graft had been used in a prior surgery in 23 cases in the rhBMP-7 group and 21 cases in the PRP group. Computer-generated randomization created 2 homogeneous groups; there were generally similar numbers of tibial, femoral, humeral, ulnar, and radial nonunions in the 2 groups. Following randomization, patients underwent surgery for nonunion, including bone grafts according to the surgeon’s choice (66.6% of rhBMP-7 patients, 80% of PRP patients). Clinical and radiologic evaluations by 1 radiologist and 2 surgeons trained in the study protocol revealed fewer unions in the platelet-rich plasma group (68%) than in the rhBMP-7 group (87%). Clinical and radiographic healing times were also found to be slower by 13% to 14% with platelet-rich plasma.

Samuel et al (2017) conducted a controlled trial in which patients with delayed unions (15 to 30 weeks old) were randomized to 2 platelet-rich plasma injections at the fracture site at baseline and 3 weeks (n=23) or no treatment (n=17).[43] The delayed unions were in the tibia (n=29), femur (n=8), forearm (n=2), and the humerus (n=1). The main outcome was long bone union, defined as no pain or tenderness on weight bearing, no abnormal mobility, and bridging at 3 or more cortices in x-ray. Examinations were conducted every 6 weeks for 36 weeks or until union. Percent union did not differ significantly between the 2 groups (78% in the platelet-rich plasma group versus 59% in the control group). Time to union also did not differ significantly (15.3 weeks for the PRP group versus 13.1 weeks for the control group).

Table 13. Summary of Key RCT Characteristics

Study	Countries	Sites	Dates	Participants	Interventions	Comparator	
					Active	Comparator 1	Comparator 2
Dallari (2007)[35]	Italy	NR	NR	Patients undergoing high tibial osteotomy to treat genu varum	Implantation of lyophilized bone chips with platelet gel (n=11)	Implantation of lyophilized bone chips with platelet gel and bone marrow stromal cells (n=12)	Implantation of lyophilized bone chips without gel (n=10)
Calori (2008)[42]	Italy	1	2005-2007	Patients undergoing treatment of long bone nonunions	PRP (n=60)	rhBMP-7 (n=60)	
Samuel (2017)[43]	India	1	2010-2014	Patients with delayed unions	PRP (n=23)	No treatment (n=17)	

NR: not reported; PRP: platelet-rich plasma; RCT: randomized controlled trial; rhBMP-7: recombinant human bone morphogenetic protein-7.

Table 14. Summary of Key RCT Results

Study	Knee Society Score at 1 yr	Knee Society Functional Score at 1 yr	Union Rate	Median Healing Time
Dallari (2007)[35,]				
PRP	91.3 ± 2	99.0 ± 0.6		
PRP+bone marrow	89.9 ± 4	99.2 ± 0.5		
Non-PRP	90.3 ± 4	98.8 ± 0.6		
Calori (2008)[42,]				
PRP			41 (68.3%)	4 ± 0.61 months
rhBMP-7			52 (86.7%)	3.5 ± 0.48
P-value			.016	
Samuel (2017)[43,]				
PRP			18 (78%)	15.3 weeks
Control			10 (59%)	13.1 weeks
P-value			.296	.54

PRP: platelet-rich plasma; RCT: randomized controlled trial; rhBMP-7: recombinant human bone morphogenetic protein-7.

Table 15. Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Follow.Up[e]
Dallari (2007)[35]	4. Only 33 patients included				
Calori (2008)[42]					
Samuel (2017)[43]					

The study limitations stated in this table are those notable in the current review; this is not a comprehensive limitations assessment.

[a] Population key: 1. Intended use population unclear; 2. Study population is unclear; 3. Study population not representative of intended use; 4, Enrolled populations do not reflect relevant diversity; 5. Other.
[b] Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest (e.g., proposed as an adjunct but not tested as such); 5: Other.
[c] Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively; 5. Other.
[d] Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. Incomplete reporting of harms; 4. Not establish and validated measurements; 5. Clinically significant difference not prespecified; 6. Clinically significant difference not supported; 7. Other.
[e] Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms; 3. Other.

Table 16. Study Design and Conduct Limitations

Study	Allocation[a]	Blinding[b]	Selective Reporting[c]	Follow Up[d]	Power[e]	Statistical[f]
Dallari (2007)[35]	3. Allocation concealment unclear	1,2,3. No blinding described			1,2. Study was underpowered and nonparametric statistical tests were performed	
Calori (2008)[42]	2. Allocation not concealed	1,2,3. No blinding described				
Samuel (2017)[43]	1. Randomization procedure not described, 3. Allocation concealment unclear	1,2,3. No blinding described				

The study limitations stated in this table are those notable in the current review; this is not a comprehensive limitations assessment.
a Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias.
b Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician.
c Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.
d Follow-Up key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials).
e Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.
f Statistical key: 1. Intervention is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Intervention is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated.

Subsection Summary: Platelet-Rich Plasma as Adjunctive Treatment for Long Bone Nonunion

Three RCTs have evaluated the efficacy of platelet-rich plasma injections in individuals with long bone nonunion. One trial with a substantial risk of bias failed to show significant differences in patient-reported or clinician-assessed functional outcome scores between patients who received platelet-rich plasma plus allogenic bone graft versus those who received

only allogenic bone graft. While the trial showed statistically significant increases in the proportion of bones that healed in patients receiving platelet-rich plasma in a modified intention-to-treat analysis, the results did not differ in the intention-to-treat analysis. An RCT that compared platelet-rich plasma with rhBMP-7 also failed to show any clinical and radiologic benefits of platelet-rich plasma over rhBMP-7. The third RCT found no difference in the number of unions or time to union in patients receiving platelet-rich plasma injections or no treatment.

Rotator Cuff Repair

Clinical Context and Therapy Purpose
The purpose of platelet-rich plasma injections plus orthopedic surgery is to provide a treatment option that is an alternative to or an improvement on existing therapies, such as orthopedic surgery alone, in individuals with rotator cuff repair.

The following PICO was used to select literature to inform this review.

Populations
The relevant population of interest is individuals with rotator cuff repair.

Interventions
The therapy being considered is platelet-rich plasma injections plus orthopedic surgery. The use of platelet-rich plasma has been proposed as a treatment for various musculoskeletal conditions and as an adjunctive procedure in orthopedic surgeries. The potential benefit of platelet-rich plasma has received considerable interest due to the appeal of a simple, safe, low-cost, and minimally invasive method of applying growth factors.

Comparators
Comparators of interest include orthopedic surgery alone.

Outcomes
The general outcomes of interest are symptoms, functional outcomes, health status measures, quality of life, morbid events, resource utilization, and treatment-related morbidity. The existing literature evaluating platelet-rich plasma injections plus orthopedic surgery as a treatment for rotator cuff repair has varying lengths of follow-up, ranging from 6 months to 3.5 years. While studies described below all reported at least 1 outcome of interest, longer follow-up was necessary to fully observe outcomes. Therefore, 3.5 years of follow-up is considered necessary to demonstrate efficacy.

Study Selection Criteria
Methodologically credible studies were selected using the principles described in the first indication.

REVIEW OF EVIDENCE

Systematic Reviews

The literature on platelet-rich plasma for rotator cuff repair consists of several RCTs and systematic reviews that have evaluated the efficacy of platelet-rich plasma membrane or matrix combined with surgical repair of the rotator cuff. The systematic reviews have varied in their outcomes of interest and findings (Tables 17 and 18).[10,36,44,45,46,47,48] For pain outcomes, systematic reviews generally found significant reductions with platelet-rich plasma at 12 months.[10,46] However, systematic review authors noted that the pain findings should be interpreted with caution due to significant residual statistical heterogeneity,[46] lack of a clinically significant difference (ie, less than the effect size threshold of 0.5 for a clinically important difference),[10] and high risk of bias in study conduct.[10,48] Some systematic reviews generally did not show a statistically or clinically significant benefit of platelet-rich plasma on other outcomes, including function, retear rate and Constant scores.[47] One systematic review found a statistically significant reduction in retear rate in a subgroup analysis of 4 long-term RCTs that were at least 24 months in duration.[48] No reviews have demonstrated a consistent statistically and clinically significant benefit of platelet-rich plasma across multiple outcomes of interest for the 3.5 years of follow-up that is considered necessary to conclusively demonstrate efficacy. The systematic review by Wang et al (2019) reported on adverse effects, that complications were only reported in 1 of the included RCTs, occurring in 5.6% of participants in the platelet-rich plasma groups and none in the control groups. The complications included infection, hematoma, and an exanthematous itchy skin lesion in 1 patient each.

Table 17. Systematic Reviews & Meta-Analysis Characteristics

Study	Dates	Trials	Participants	N (Range)	Design	Duration
Li (2021)[48]	Through Oct 2020	16 (PRP)	Patients undergoing surgery for rotator cuff repair	1440 (28 to 120)	RCT	1.5 to 60 mo
Chen (2020)[47]	2011-2017	17	Patients with rotator cuff tears	1116[a] (36 to 120)	RCT	NR
Johal (2019)[10]	2011-2016	13	Patients undergoing surgery for rotator cuff repair	858 (25 to 120)	RCT	7w to 24mo
Chen (2017)[46]	2011-2016	37	Patients with tendon and ligament injuries	1031[a] (NR)	RCT	NR
Fu (2017)[49]	2011-2015	11	Patients with rotator cuff injury or tendinopathy	638 (NR)	RCT	NR
Zhao (2015)[44]	2011-2013	8	Patients with rotator cuff injury	464 (28 to 88)	RCT	NR
Moraes (2014)[36]	2008-2013	19	Patients undergoing rotator cuff repair	1088 (23 to 150)	RCT and quasi-randomized trials	NR

NR: not reported; RCT: randomized controlled trial.
aNumber of participants from the 21 articles which could be included in the quantitative analysis.

Table 18. Systematic Reviews & Meta-Analysis Results

Study	VAS Reduction	VAS Reduction at 1 Year	Difference in Retear Rate	Difference in Function	Difference in Function at 1 Year
Li (2021) [48]	10 RCTs; n=559		12 RCTs; n=700 RCTs ≥24 months: 4 RCTs, n=255	UCLA Score: 7 RCTs; n=437	
Point estimate	10 RCTs: MD -0.13		12 RCTs: RR, 0.56 RCTs ≥24 months: RR, 0.40	7 RCTs: MD, 1.55	
95% CI	10 RCTs: -0.56 to -0.06		12 RCTs: RR, 0.56 RCTs ≥24 months: 0.22 to 0.73	7 RCTs: MD, 0.86 to 2.24	
Chen (2020)[47]		8 RCTs; N=469			UCLA Score: 6 RCTs; N=386
WMD		-0.34			1.39
95% CI		-0.76, 0.09			0.35, 2.43
I^2		87.5%			37.8%
Johal (2019[10]		7 RCTs, N=324			
SMD		-0.261			
95% CI		-0.46, -0.05			
I^2		0%			
Chen (2018)[46]					
WMD		-0.84			
95% CI		-1.23 to -0.44			
P-value		<.01			
Fu (2017)[49]					
SMD		0.142[a]			
95% CI		-0.08 to 0.364			
P-value		.209			
Zhao (2015)[44]					
RR			0.94		
95% CI			0.70 to 1.25		
P-value			.66		
Moraes (2013)[36]					

SMD					0.25
95% CI					-0.07 to 0.57
P-value					.12

[a] Change from baseline at final follow-up. Follow-up durations ranged from 6 weeks to 24 months.
CI: confidence interval; RCT: randomized controlled trial; RR: risk ratio; SMD: standard mean difference; UCLA: University of California at Los Angeles (UCLA) activity score; VAS: visual analog scale; WMD: weighted mean difference.

Randomized Controlled Trials

Data from a 2011 double-blind RCT by Randelli et al that included 53 patients randomized to receive arthroscopic rotator cuff repair with or without the addition of platelet-rich plasma is included in multiple meta-analyses summarized above. Randelli et al (2021) published results of a 10-year follow-up of this trial, which included data for 17 patients who received platelet-rich plasma and 21 control group patients.[50] At the 10-year follow-up, both platelet-rich plasma and control groups experienced improvements in the median (interquartile range [IQR]) University of California at Los Angeles activity score (34 [29 to 35] and 33 [29 to 35] points, respectively) and VAS score (0.34 [0 to 1.85] and 0.70 [0 to 2.45] points, respectively); the between-group differences did not reach statistical significance. Furthermore, approximately 37% of the operated patients had a re-rupture in each group. Retears occurred in 6% of the patients who received platelet-rich plasma treatment and 14% of patients in the control group (p=.61).

Subsection Summary: Platelet-Rich Plasma as Adjunctive Treatment for Rotator Cuff Repair

For individuals undergoing rotator cuff repair who receive platelet-rich plasma injections, the evidence includes multiple systematic reviews with meta-analyses and an RCT. Relevant outcomes include symptoms, functional outcomes, health status measures, quality of life, morbid events, resource utilization, and treatment-related morbidity. Although systematic reviews consistently found significant reductions in pain with platelet-rich plasma at 12 months, important study conduct and relevance weaknesses limit interpretation of these findings. While the systematic reviews and meta-analyses generally failed to show a statistically and/or clinically significant impact on other outcomes, 1 meta-analysis found a statistically significant reduction in retear rate in a subgroup analysis of 4 RCTs that were at least 24 months in duration. Findings of a subsequently published 10-year follow-up of a small RCT failed to demonstrate the superiority of platelet-rich plasma over control for clinical and radiologic outcomes. The variability in platelet-rich plasma preparation techniques and platelet-rich plasma administration limit the generalizability of the available evidence.

Spinal Fusion

Clinical Context and Therapy Purpose

The purpose of platelet-rich plasma injections plus orthopedic surgery is to provide a treatment option that is an alternative to or an improvement on existing therapies, such as orthopedic surgery alone, in individuals with spinal fusion.

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is individuals with spinal fusion.

Interventions
The therapy being considered is platelet-rich plasma injections plus orthopedic surgery. The use of platelet-rich plasma has been proposed as a treatment for various musculoskeletal conditions and as an adjunctive procedure in orthopedic surgeries. The potential benefit of platelet-rich plasma has received considerable interest due to the appeal of a simple, safe, low-cost, and minimally invasive method of applying growth factors.

Comparators
Comparators of interest include orthopedic surgery alone.

Outcomes
The general outcomes of interest are symptoms, functional outcomes, health status measures, quality of life, morbid events, resource utilization, and treatment-related morbidity. The existing literature evaluating platelet-rich plasma injections plus orthopedic surgery as a treatment for spinal fusion has varying lengths of follow-up.

Study Selection Criteria
Methodologically credible studies were selected using the principles described in the first indication.

REVIEW OF EVIDENCE

Randomized Controlled Trials

One small (N=62), unblinded, single-center RCT for spinal fusion conducted in Japan and published by Kubota et al (2019) was identified that compared platelet-rich plasma to no platelet-rich plasma.[51] Follow-up was 24 months. Although fusion rates were significantly improved with platelet-rich plasma, there were no significant differences in visual analog scale scores between the 2 groups. Major limitations of this RCT include that patients were unblinded to treatment and there was no placebo comparator.

Prospective Cohort Studies

Two prospective observational studies found no differences in fusion rates with the use of a platelet gel or platelet glue compared with historical controls.[52,53]

Subsection Summary: Platelet-Rich Plasma as Adjunctive Treatment for Spinal Fusion
For individuals undergoing spinal fusion who receive platelet-rich plasma injections, the evidence includes a single small RCT and two observational studies. Relevant outcomes include symptoms, functional outcomes, health status measures, quality of life, morbid events, resource utilization, and treatment-related morbidity. Studies have generally failed to show a statistically and/or clinically significant impact on symptoms (ie, pain).

Subacromial Decompression Surgery

Clinical Context and Therapy Purpose

The purpose of platelet-rich plasma injections plus orthopedic surgery is to provide a treatment option that is an alternative to or an improvement on existing therapies, such as orthopedic surgery alone, in individuals with subacromial decompression surgery.

The following PICO was used to select literature to inform this review.

Populations
The relevant population of interest are individuals with subacromial decompression surgery.

Interventions
The therapy being considered is platelet-rich plasma injections plus orthopedic surgery. The use of platelet-rich plasma has been proposed as a treatment for various musculoskeletal conditions and as an adjunctive procedure in orthopedic surgeries. The potential benefit of platelet-rich plasma has received considerable interest due to the appeal of a simple, safe, low-cost, and minimally invasive method of applying growth factors.

Comparators
Comparators of interest include orthopedic surgery alone.

Outcomes
The general outcomes of interest are symptoms, functional outcomes, health status measures, quality of life, morbid events, resource utilization, and treatment-related morbidity. The existing literature evaluating platelet-rich plasma injections plus orthopedic surgery as a treatment for subacromial decompression surgery has varying lengths of follow-up. While studies described below all reported at least 1 outcome of interest, longer follow-up was necessary to fully observe outcomes.

Study Selection Criteria
Methodologically credible studies were selected using the principles described in the first indication.

REVIEW OF EVIDENCE

Randomized Controlled Trials

One small RCT evaluated the use of PRP as an adjunct to subacromial decompression surgery. Everts et al (2008) reported on a rigorously conducted, small (N=40) double-blinded RCT of platelet and leukocyte-rich plasma gel following open subacromial decompression surgery in a carefully selected patient population.[54] Neither self-assessed nor physician-assessed instability improved. Both subjective pain and use of pain medication were lower in the platelet and leukocyte-rich plasma group across the 6 weeks of measurements. For example, at 2 weeks after surgery, VAS scores for pain were lower by about 50% in the platelet and leukocyte-rich group (close to 4 in the control group, close to 2 in the platelet and leukocyte-rich group), and only 1 (5%) patient in the platelet and leukocyte-rich group was taking pain medication compared with 10 (50%) control patients. Objective measures of range of motion showed clinically significant improvements in the platelet and leukocyte-rich group across the 6-week assessment period, with patients reporting improvements in activities of

daily living, such as the ability to sleep on the operated shoulder at 4 weeks after surgery and earlier return to work.

Subsection Summary: Platelet-Rich Plasma as Adjunctive Treatment for Subacromial Decompression Surgery
A single small RCT has evaluated the efficacy of platelet-rich plasma injections in individuals undergoing subacromial decompression surgery. Compared with controls, platelet-rich plasma treatment did not improve self-assessed or physician-assessed instability. However, subjective pain, use of pain medication, and objective measures of range of motion showed clinically significant improvements with platelet-rich plasma. Larger RCTs would be required to confirm these benefits.

Total Knee Arthroplasty

Clinical Context and Therapy Purpose
The purpose of platelet-rich plasma injections plus orthopedic surgery is to provide a treatment option that is an alternative to or an improvement on existing therapies, such as orthopedic surgery alone, in individuals with total knee arthroplasty (TKA).

The following PICO was used to select literature to inform this review.

Populations
The relevant population of interest is individuals with TKA.

Interventions
The therapy being considered is platelet-rich plasma injections plus orthopedic surgery. The use of platelet-rich plasma has been proposed as a treatment for various musculoskeletal conditions and as an adjunctive procedure in orthopedic surgeries. The potential benefit of platelet-rich plasma has received considerable interest due to the appeal of a simple, safe, low-cost, and minimally invasive method of applying growth factors.

Comparators
Comparators of interest include orthopedic surgery alone.

Outcomes
The general outcomes of interest are symptoms, functional outcomes, health status measures, quality of life, morbid events, resource utilization, and treatment-related morbidity. The existing literature evaluating platelet-rich plasma injections plus orthopedic surgery as a treatment for total knee arthroplasty has varying lengths of follow-up. While studies described below all reported at least 1 outcome of interest, longer follow-up was necessary to fully observe outcomes.

Study Selection Criteria
Methodologically credible studies were selected using the principles described in the first indication.

REVIEW OF EVIDENCE

Systematic Reviews

Trams et al (2020) published a systematic review and meta-analysis that included 6 RCTs (N=621) evaluating the effects of intraoperative platelet-rich plasma as an adjunct to total knee arthroplasty.[19] Two studies were deemed at high risk of bias. The primary aim of the studies was to assess blood loss during the procedure. While there were significant differences in favor of platelet-rich plasma in the overall effect on blood parameters in comparison to the control groups (standard MD, -0.29; 95% CI, -0.46 to -0.11), no significant differences in range of motion, functional outcomes, or long-term pain were observed.

Shu et al (2022) evaluated platelet-rich plasma in patients undergoing total joint replacement including 8 studies in patients with total knee arthroplasty (1 study for total hip arthroplasty and 1 on total hip or knee arthroplasty).[55] Of the 3 studies reporting VAS scores in patients undergoing total knee arthroplasty (n=161), pain scores were similar during the first 2 postoperative days, but by 3 weeks and 2 months had improved with platelet-rich plasma compared with control (MD, -0.92; 95% CI, -1.25 to -0.60 and -0.93; 95% CI, -1.24 to -0.63, respectively). There were no differences in range of motion, WOMAC scores, length of hospital stay, or wound healing within 4 weeks between platelet-rich plasma or controls in patients undergoing total knee arthroplasty. The authors noted high heterogeneity and the need for more high-quality RCTs.

Subsection Summary: Platelet-Rich Plasma as Adjunctive Treatment for Total Knee Arthroplasty

A single systematic review has evaluated the efficacy of intraoperative platelet-rich plasma injections in individuals undergoing total knee arthroplasty. In the review by Trams et al (2020) there were no significant differences between the platelet-rich plasma and untreated control groups across several functional and pain outcomes. The systematic review by Shu et al (2022) found improved VAS scores in patients undergoing total knee arthroplasty; however, there were no differences in other outcomes and the authors noted high heterogeneity and the need for well-designed RCTs.

SUMMARY OF EVIDENCE

Primary Treatment for Tendinopathies

For individuals with tendinopathy who receive platelet-rich plasma injections, the evidence includes multiple randomized controlled trials (RCTs) and systematic reviews with meta-analyses. Relevant outcomes are symptoms, functional outcomes, health status measures, quality of life, and treatment-related morbidity. Findings from meta-analyses of RCTs have been mixed and have generally found that platelet-rich plasma did not have a statistically and/or clinically significant impact on symptoms (ie, pain) or functional outcomes. Findings from a subsequently published RCT failed to find improvement compared with placebo. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Primary Treatment for Non-Tendon Soft Tissue Injury or Inflammation

For individuals with non-tendon soft tissue injury or inflammation (eg, plantar fasciitis) who receive platelet-rich plasma injections, the evidence includes several small RCTs, multiple prospective observational studies, and systematic reviews. Relevant outcomes are symptoms, functional outcomes, health status measures, quality of life, and treatment-related morbidity.

The 2014 systematic review, which identified 3 RCTs on platelet-rich plasma for plantar fasciitis, did not pool study findings. Results among the remaining RCTs were inconsistent. The largest RCT showed that treatment using platelet-rich plasma compared with corticosteroid injection resulted in statistically significant improvement in pain and disability, but not quality of life. A 2023 systematic review found improved visual analog scale scores with platelet-rich plasma compared to corticosteroid injections out to 6 months duration, but numerical differences between groups were small. Larger RCTs completed over a sufficient duration of time (ie, 2 years) are still needed to address important uncertainties in efficacy and safety. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Primary Treatment for Osteochondral Lesions

For individuals with osteochondral lesions who receive platelet-rich plasma injections, the evidence includes an open-labeled quasi-randomized study. Relevant outcomes are symptoms, functional outcomes, health status measures, quality of life, and treatment-related morbidity. The quasi-randomized study found a statistically significant greater impact on outcomes in the platelet-rich plasma group than in the hyaluronic acid group. Limitations of the evidence base include lack of adequately randomized studies, lack of blinding, lack of sham controls, and comparison only to an intervention of uncertain efficacy. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Primary Treatment for Knee or Hip Osteoarthritis

For individuals with knee or hip osteoarthritis who receive platelet-rich plasma injections, the evidence includes multiple RCTs and systematic reviews. Relevant outcomes are symptoms, functional outcomes, health status measures, quality of life, and treatment-related morbidity. Most trials have compared platelet-rich plasma with hyaluronic acid for knee osteoarthritis. Systematic reviews have generally found that platelet-rich plasma was more effective than placebo or hyaluronic acid in reducing pain and improving function. However, systematic review authors have noted that their findings should be interpreted with caution due to important limitations including significant residual statistical heterogeneity, questionable clinical significance, and high risk of bias in study conduct. RCTs with a follow-up of at least 12 months published subsequent to the systematic reviews found statistically significantly greater 12-month reductions in pain and function outcomes, but these findings were also limited by important study conduct flaws including potential inadequate control for selection bias and limited or unclear blinding. Also, benefits were not maintained at 5 years. Using hyaluronic acid as a comparator is questionable because the evidence demonstrating the benefit of hyaluronic acid treatment for osteoarthritis is not robust. Two systematic reviews evaluating hip osteoarthritis did not report any statistically or clinically significant differences in pain or functional outcomes compared to hyaluronic acid, corticosteroids or placebo. Additional studies comparing platelet-rich plasma with placebo and with alternatives other than hyaluronic acid are needed to determine the efficacy of platelet-rich plasma for knee and hip osteoarthritis. Studies are also needed to determine the optimal protocol for delivering platelet-rich plasma. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Adjunct to Surgery

For individuals with anterior cruciate ligament reconstruction who receive platelet-rich plasma injections plus orthopedic surgery, the evidence includes several systematic reviews of multiple RCTs and prospective studies and a retrospective matched case-control study. Relevant outcomes are symptoms, functional outcomes, health status measures, quality of life, morbid events, resource utilization, and treatment-related morbidity. In 2 systematic reviews that conducted a meta-analysis, adjunctive platelet-rich plasma treatment did not result in a significant effect on International Knee Documentation Committee (IKDC) scores, a patient-reported, knee-specific outcome measure that assesses pain and functional activity. One systematic review found improvements with platelet-rich plasma compared to controls in outcomes at 6 months, but these differences were determined to be clinically irrelevant with the exception of pain at 6 months which was improved with platelet-rich plasma. Individual trials have shown mixed results. A retrospective matched case-control study found no differences in knee function scores or time to return of activity between platelet-rich plasma and matched-control groups at 2 years; however, the platelet-rich plasma group demonstrated a higher rate of postoperative knee motion loss compared with the control group. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with hip fracture who receive platelet-rich plasma injections plus orthopedic surgery, the evidence includes an open-labeled RCT. Relevant outcome are symptoms, functional outcomes, health status measures, quality of life, morbid events, resource utilization, and treatment-related morbidity. The single open-label RCT failed to show a statistically significant reduction in the need for surgical revision with the addition of platelet-rich plasma treatment. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with long bone nonunion who receive platelet-rich plasma injections plus orthopedic surgery, the evidence includes 3 RCTs. Relevant outcomes are symptoms, functional outcomes, health status measures, quality of life, morbid events, resource utilization, and treatment-related morbidity. One trial with a substantial risk of bias failed to show significant differences in patient-reported or clinician-assessed functional outcome scores between those who received platelet-rich plasma plus allogenic bone graft and those who received only allogenic bone graft. While the trial showed a statistically significant increase in the proportion of bones that healed in patients receiving platelet-rich plasma in a modified intention-to-treat analysis, the results did not differ in the intention-to-treat analysis. An RCT that compared platelet-rich plasma with recombinant human bone morphogenetic protein-7 (rhBMP-7) also failed to show any clinical or radiologic benefits of platelet-rich plasma over morphogenetic protein. The third RCT found no difference in the number of unions or time to union in patients receiving platelet-rich plasma injections or no treatment. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with rotator cuff repair who receive platelet-rich plasma injections plus orthopedic surgery, the evidence includes multiple RCTs and systematic reviews. Relevant outcomes are symptoms, functional outcomes, health status measures, quality of life, morbid events, resource utilization, and treatment-related morbidity. Although systematic reviews consistently found significant reductions in pain with platelet-rich plasma at 12 months, important study conduct and relevance weaknesses limit interpretation of these findings. While

the systematic reviews and meta-analyses generally failed to show a statistically and/or clinically significant impact on other outcomes, 1 meta-analysis found a statistically significant reduction in retear rate in a subgroup analysis of 4 RCTs that were at least 24 months in duration. The findings of a subsequently published 10-year follow-up of a small RCT failed to demonstrated the superiority of platelet-rich plasma over control for clinical and radiologic outcomes. The variability in platelet-rich plasma preparation techniques and platelet-rich plasma administration limits the generalizability of the available evidence. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals undergoing spinal fusion who receive platelet-rich plasma injections plus orthopedic surgery, the evidence includes a single small RCT and a few observational studies. Relevant outcomes include symptoms, functional outcomes, health status measures, quality of life, morbid events, resource utilization, and treatment-related morbidity. Studies have generally failed to show a statistically and/or clinically significant impact on symptoms (ie, pain). The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with subacromial decompression surgery who receive platelet-rich plasma injections plus orthopedic surgery, the evidence includes a small RCT. Relevant outcomes are symptoms, functional outcomes, health status measures, quality of life, morbid events, resource utilization, and treatment-related morbidity. A single small RCT failed to show a reduction in self-assessed or physician-assessed spinal instability scores with platelet-rich plasma injections. However, subjective pain, use of pain medications, and objective measures of range of motion showed clinically significant improvements with PRP. Larger trials are required to confirm these benefits. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with total knee arthroplasty who receive platelet-rich plasma injections plus orthopedic surgery, the evidence includes systematic reviews. Relevant outcomes are symptoms, functional outcomes, health status measures, quality of life, morbid events, resource utilization, and treatment-related morbidity. The reviews showed no significant differences between the platelet-rich plasma and untreated control groups in range of motion, functional outcomes, and long-term pain. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

SUPPLEMENTAL INFORMATION

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in ‘Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

American Academy of Orthopaedic Surgeons

In 2021, the American Academy of Orthopaedic Surgeons (AAOS) guidelines for the management of osteoarthritis of the knee made the following recommendation:[56]

- "Platelet-rich plasma (PRP) may reduce pain and improve function in patients with symptomatic osteoarthritis of the knee. (Strength of Recommendation: Limited)" The variability of study findings was noted to have contributed to the low strength of recommendation rating.

In 2023, the AAOS updated evidence-based guidelines on the management of osteoarthritis of the hip.[57] In the section on intra-articular injectables, the guidelines gave a moderate recommendation based on high-quality evidence supporting the use of intra-articular corticosteroids as an option to improve function and reduce pain in the short term for patients with osteoarthritis of the hip. There was also a strong recommendation based on high-quality evidence against the use of intra-articular hyaluronic acid, as it does not perform better than placebo in improving function, stiffness, and pain in patients with hip osteoarthritis. The guidelines did not mention any evidence or make recommendations related to the use of platelet-rich plasma for the treatment of osteoarthritis of the hip.

In 2019, the AAOS issued evidence-based guidelines on the management of rotator cuff injuries.[58] The guideline noted the following recommendations related to the use of platelet-rich plasma in this setting:

- "There is limited evidence supporting the routine use of platelet-rich plasma for the treatment of cuff tendinopathy or partial tears (Strength of Recommendation: Limited)." The variability of study findings was noted to have contributed to the low strength of recommendation rating.
- "Strong evidence does not support biological augmentation of rotator cuff repair with platelet-derived products on improving patient reported outcomes; however, limited evidence supports the use of liquid platelet rich plasma in the context of decreasing re-tear rates (Strength of Recommendation: Strong)."
- "In the absence of reliable evidence, it is the consensus of the work group that we do not recommend the routine use of platelet rich plasma in the non-operative management of full-thickness rotator cuff tears. (Strength of Recommendation: Consensus)"

National Institute for Health and Clinical Excellence

In 2013, the NICE issued guidance on use of autologous blood injection for tendinopathy.[59] The NICE concluded that the current evidence on the safety and efficacy of autologous blood injection for tendinopathy was “inadequate” in quantity and quality.

In 2013, the NICE also issued guidance on use of autologous blood injection (with or without techniques for producing platelet-rich plasma) for plantar fasciitis.[60] The NICE concluded that the evidence on autologous blood injection for plantar fasciitis raised no major safety concerns but that the evidence on efficacy was “inadequate in quantity and quality.”

In 2019, the NICE issued guidance on use of platelet-rich plasma for osteoarthritis of the knee.[61] The NICE concluded that current evidence on platelet-rich plasma injections for osteoarthritis of the knee raised “no major safety concerns”; however, the “evidence on

efficacy is limited in quality." Therefore, the NICE recommended that "this procedure should only be used with special arrangements form clinical governance, consent, and audit or research."

U.S. Preventive Services Task Force Recommendations
Not applicable.

Ongoing and Unpublished Clinical Trials
Some currently unpublished trials that might influence this review are listed in Table 19.

Table 19. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT05742763[a]	Platelet-Rich Plasma and the Effects of NSAIDs on Pain and Functional Scores in Knee Osteoarthritis	300	Dec 2027
NCT05742061	Intra-articular Platelet Rich Plasma vs Corticosteroid in Treatment of Knee Osteoarthritis	100	Dec 2023
NCT03734900	Comparison of Effectiveness Between Platelet Lysate and Platelet-rich Plasma on Knee Osteoarthritis: a Prospective, Randomized, Placebo-controlled Trial	150	May 2022 (recruiting)
NCT03984955	A Prospective, Double Blind, Single Centre, RCT, Comparing the Effectiveness of Physiotherapy in Addition to One of 3 Types of Image Guided Injection of the Common Extensor Tendon, on Pain and Function in Patients With Tennis Elbow	123	Apr 2024
NCT01843504	The Clinical, Biomechanical, and Tissue Regenerating Effects of a Single Platelet-rich Plasma Injection for the Treatment of Chronic Patellar Tendinopathy: a Randomized Controlled Trial	44	Dec 2023 (recruiting)
Unpublished			
NCT04697667	The Combination of Exercise and PRP vs Exercise Alone in Patients With Knee Osteoarthritis: A Randomized Controlled Clinical Trial	84	Feb 2022
NCT04703998	Arthroscopic Rotator Cuff Repair Augmented With Platelet Rich Plasma	103	Sep 2022

NCT: national clinical trial
[a] Denotes industry-sponsored or cosponsored trial.

Government Regulations
National:
There is no national coverage determination (NCD) on this topic.

Local:
There is no local coverage determination (LCD) on this topic.

(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicare Services [CMS, formerly HCFA] are updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. For the most current information, the reader should contact an official Medicare source.)

Related Policies

- Orthopedic Applications of Stem Cell Therapy (Including autologous stem cells used with Allografts and Bone Substitutes)
- Prolotherapy
- Platelet Rich Plasma Autologous Platelet-Derived Growth Factors as a Treatment of Wound Healing and Other Non-Orthopedic Conditions

References

1. Crovetti G, Martinelli G, Issi M, et al. Platelet gel for healing cutaneous chronic wounds. Transfus Apher Sci. Apr 2004;30(2):145-151. PMID 15062754
2. Eppley BL, Woodell JE, Higgins J. Platelet quantification and growth factor analysis from platelet-rich plasma: implications for wound healing. Plast Reconstr Surg. Nov 2004; 114(6): 1502-1508. PMID 15509939
3. Kevy SV, Jacobson MS. Comparison of methods for point of care preparation of autologous platelet gel. J Extra Corpor Technol. Mar 2004;36(1):28-35. PMID 15095838
4. Castillo TN, Pouliot MA, Kim HJ, et al. Comparison of growth factor and platelet concentration from commercial platelet-rich plasma separation systems. Am J Sports Med. Feb 2011;39(2):266-271. PMID 21051428
5. Mazzucco L, Balbo V, Cattana E, et al. Not every PRP-gel is born equal. Evaluation of growth factor availability for tissues through four PRP-gel preparations: Fibrinet, RegenPRP-Kit, Plateltex and one manual procedure. Vox Sang. Aug 2009;97(2):110-118. PMID 19392780
6. Hsu WK, Mishra A, Rodeo SR, et al. Platelet-rich Plasma in Orthopaedic Applications: Evidence-Based Recommendations for Treatment. J Am Acad Orthop Surg. Dec 2013; 21(12) 739-48. PMID 24292930
7. Masiello F, Pati I, Veropalumbo E, et al. Ultrasound-guided injection of platelet-rich plasma for tendinopathies: a systematic review and meta-analysis. Blood Transfus. Oct 17 2022. PMID 36346880
8. Dai W, Yan W, Leng X, et al. Efficacy of Platelet-Rich Plasma Versus Placebo in the Treatment of Tendinopathy: A Meta-analysis of Randomized Controlled Trials. Clin J Sport Med. Aug 02 2021. PMID 34342296
9. Muthu S, Patel S, Gobbur A, et al. Platelet-rich plasma therapy ensures pain reduction in the management of lateral epicondylitis - a PRISMA-compliant network meta-analysis of randomized controlled trials. Expert Opin Biol Ther. Jan 31 2022: 1-12. PMID 35078375
10. Johal H, Khan M, Yung SP et al. Impact of platelet-rich plasma use on pain in orthopaedic surgery: a systematic review and meta-analysis. Sports Health. 2019 Jul;11(4). PMID 31136726
11. Kearney RS, Ji C, Warwick J, et al. Effect of Platelet-Rich Plasma Injection vs Sham Injection on Tendon Dysfunction in Patients With Chronic Midportion Achilles Tendinopathy: A Randomized Clinical Trial. JAMA. Jul 13 2021; 326(2): 137-144. PMID 34255009
12. Seth I, Bulloch G, Seth N, et al. The role of corticosteroid injections in treating plantar fasciitis: A systematic review and meta-analysis. Foot (Edinb). Mar 2023; 54: 101970. PMID 36774828

13. Peerbooms JC, Lodder P, den Oudsten BL et al. Positive effect of platelet-rich plasma on pain in plantar fasciitis: a double-blind multicenter randomized controlled trial. Am J Sports Med. 2019 Nov;47(13). PMID 31603721
14. Shetty SH, Dhond A, Arora M, et al. Platelet-rich plasma has better long-term results than corticosteroids or placebo for chronic plantar fasciitis: randomized control trial. J Foot Ankle Surg. Jan 2019;58(1):42-46. PMID 30448183
15. Johnson-Lynn S, Cooney A, Ferguson D et al. A feasibility study comparing platelet-rich plasma injection with saline for the treatment of plantar fasciitis using a prospective, randomized trial design. Foot Ankle Spec. 2019 Apr;12(2). PMID 29779399
16. Tabrizi A, Dindarian S, Mohammadi S. The Effect of Corticosteroid Local Injection Versus Platelet-Rich Plasma for the Treatment of Plantar Fasciitis in Obese Patients: A Single-Blind, Randomized Clinical Trial. J Foot Ankle Surg. Jan 2020; 59(1): 64-68. PMID 31882151
17. Mei-Dan O, Carmont MR, Laver L, et al. Platelet-rich plasma or hyaluronate in the management of osteochondral lesions of the talus. Am J Sports Med. Mar 2012;40(3):534-541. PMID 22253252
18. Anil U, Markus DH, Hurley ET, et al. The efficacy of intra-articular injections in the treatment of knee osteoarthritis: A network meta-analysis of randomized controlled trials. Knee. Oct 2021; 32: 173-182. PMID 34500430
19. Trams E, Kulinski K, Kozar-Kaminska K, et al. The Clinical Use of Platelet-Rich Plasma in Knee Disorders and Surgery-A Systematic Review and Meta-Analysis. Life (Basel). Jun 25 2020; 10(6). PMID 32630404
20. Laudy AB, Bakker EW, Rekers M, et al. Efficacy of platelet-rich plasma injections in osteoarthritis of the knee: a systematic review and meta-analysis. Br J Sports Med. May 2015;49(10):657-672. PMID 25416198
21. Chang KV, Hung CY, Aliwarga F, et al. Comparative Effectiveness of Platelet-Rich Plasma Injections for Treating Knee Joint Cartilage Degenerative Pathology: A Systematic Review and Meta-Analysis. Arch Phys Med Rehabil. Mar 2014;95(3):562-575. PMID 24291594
22. Meheux CJ, McCulloch PC, Lintner DM, et al. Efficacy of intra-articular platelet-rich plasma injections in knee osteoarthritis: a systematic review. Arthroscopy. Mar 2016;32(3):495-505. PMID 26432430
23. Lai LP, Stitik TP, Foye PM, et al. Use of platelet-rich plasma in intra-articular knee injections for osteoarthritis: a systematic review. PM R. Jun 2015;7(6):637-648. PMID 25687110
24. Cole BJ, Karas V, Hussey K, et al. Hyaluronic acid versus platelet-rich plasma. Am J Sports Med. Feb 2017;45(2):339-346. PMID 28146403
25. Duymus TM, Mutlu S, Dernek B, et al. Choice of intra-articular injection in treatment of knee osteoarthritis: platelet-rich plasma, hyaluronic acid or ozone options. Knee Surg Sports Traumatol Arthrosc. Feb 2017;25(2):485-492. PMID 27056686
26. Kanchanatawan W, Arirachakaran A, Chaijenkij K, et al. Short-term outcomes of platelet-rich plasma injection for treatment of osteoarthritis of the knee. Knee Surg Sports Traumatol Arthrosc. May 2016;24(5):1665-1677. PMID 26387122
27. Xu Z, Luo J, Huang X, et al. Efficacy of platelet-rich plasma in pain and self-report function in knee osteoarthritis: a best-evidence synthesis. Am J Phys Med Rehabil. Nov 2017;96(11):793-800. PMID 28398969
28. Belk JW, Houck DA, Littlefield CP, et al. Platelet-Rich Plasma Versus Hyaluronic Acid for Hip Osteoarthritis Yields Similarly Beneficial Short-Term Clinical Outcomes: A Systematic

Review and Meta-Analysis of Level I and II Randomized Controlled Trials. Arthroscopy. Nov 14 2021. PMID 34785294
29. Gazendam A, Ekhtiari S, Bozzo A, et al. Intra-articular saline injection is as effective as corticosteroids, platelet-rich plasma and hyaluronic acid for hip osteoarthritis pain: a systematic review and network meta-analysis of randomised controlled trials. Br J Sports Med. Mar 2021; 55(5): 256-261. PMID 32829298
30. Sdeek M, Sabry D, El-Sdeek H, et al. Intra-articular injection of Platelet rich plasma versus Hyaluronic acid for moderate knee osteoarthritis. A prospective, double-blind randomized controlled trial on 189 patients with follow-up for three years. Acta Orthop Belg. Dec 2021; 87(4): 729-734. PMID 35172440
31. Reyes-Sosa R, Lugo-Radillo A, Cruz-Santiago L, et al. Clinical comparison of platelet-rich plasma injection and daily celecoxib administration in the treatment of early knee osteoarthritis: a randomized clinical trial. J Appl Biomed. 2020;18(2-3):41-45. doi: 10.32725/jab.2020.012.
32. Elksniņš-Finogejevs A, Vidal L, Peredistijs A. Intra-articular platelet-rich plasma vs corticosteroids in the treatment of moderate knee osteoarthritis: a single-center prospective randomized controlled study with a 1-year follow up. J Orthop Surg Res. Jul 10 2020; 15(1): 257. PMID 32650801
33. Dallari D, Stagni C, Rani N, et al. Ultrasound-guided injection of platelet-rich plasma and hyaluronic acid, separately and in combination, for hip osteoarthritis: a randomized controlled study. Am J Sports Med. Mar 2016;44(3):664-671. PMID 26797697
34. Nouri F, Babaee M, Peydayesh P, et al. Comparison between the effects of ultrasound guided intra-articular injections of platelet-rich plasma (PRP), high molecular weight hyaluronic acid, and their combination in hip osteoarthritis: a randomized clinical trial. BMC Musculoskelet Disord. Sep 12 2022; 23(1): 856. PMID 36096771
35. Dallari D, Savarino L, Stagni C, et al. Enhanced tibial osteotomy healing with use of bone grafts supplemented with platelet gel or platelet gel and bone marrow stromal cells. J Bone Joint Surg Am. Nov 2007;89(11):2413-2420. PMID 17974883
36. Moraes VY, Lenza M, Tamaoki MJ, et al. Platelet-rich therapies for musculoskeletal soft tissue injuries. Cochrane Database Syst Rev. Dec 23 2013;12(12):CD010071. PMID 24363098
37. Lv ZT, Zhang JM, Pang ZY, et al. The efficacy of platelet rich plasma on anterior cruciate ligament reconstruction: a systematic review and meta-analysis. Platelets. Feb 17 2022; 33(2): 229-241. PMID 34048294
38. Nin JR, Gasque GM, Azcarate AV, et al. Has platelet-rich plasma any role in anterior cruciate ligament allograft healing? Arthroscopy. Nov 2009;25(11):1206-1213. PMID 19896041
39. Bailey L, Weldon M, Kleihege J, et al. Platelet-Rich Plasma Augmentation of Meniscal Repair in the Setting of Anterior Cruciate Ligament Reconstruction. Am J Sports Med. Oct 2021; 49(12): 3287-3292. PMID 34477016
40. Griffin XL, Achten J, Parsons N, et al. Platelet-rich therapy in the treatment of patients with hip fractures: a single centre, parallel group, participant-blinded, randomised controlled trial. BMJ Open. 2013;3(6). PMID 23801709
41. Griffin XL, Wallace D, Parsons N, et al. Platelet rich therapies for long bone healing in adults. Cochrane Database Syst Rev. 2012;7:CD009496. PMID 22786528
42. Calori GM, Tagliabue L, Gala L, et al. Application of rhBMP-7 and platelet-rich plasma in the treatment of long bone non-unions: a prospective randomised clinical study on 120 patients. Injury. Dec 2008;39(12):1391-1402. PMID 19027898

43. Samuel G, Menon J, Thimmaiah S, et al. Role of isolated percutaneous autologous platelet concentrate in delayed union of long bones. Eur J Orthop Surg Traumatol. Nov 22 2017. PMID 29167980
44. Zhao JG, Zhao L, Jiang YX, et al. Platelet-rich plasma in arthroscopic rotator cuff repair: a meta-analysis of randomized controlled trials. Arthroscopy. Jan 2015;31(1):125-135. PMID 25278352
45. Yang J, Sun Y, Xu P, et al. Can patients get better clinical outcomes by using PRP in rotator cuff repair: a meta-analysis of randomized controlled trials. J Sports Med Phys Fitness. Oct 16 2015. PMID 26473444
46. Chen X, Jones IA, Park C, et al. The efficacy of platelet-rich plasma on tendon and ligament healing: a systematic review and meta-analysis with bias assessment. Am J Sports Med. Dec 1 2017:363546517743746. PMID 29268037
47. Chen X, Jones IA, Togashi R, et al. Use of Platelet-Rich Plasma for the Improvement of Pain and Function in Rotator Cuff Tears: A Systematic Review and Meta-analysis With Bias Assessment. Am J Sports Med. Jul 2020; 48(8): 2028-2041. PMID 31743037
48. Li Y, Li T, Li J, et al. Platelet-Rich Plasma Has Better Results for Retear Rate, Pain, and Outcome Than Platelet-Rich Fibrin After Rotator Cuff Repair: A Systematic Review and Meta-analysis of Randomized Controlled Trials. Arthroscopy. Feb 2022; 38(2): 539-550. PMID 34052384
49. Fu CJ, Sun JB, Bi ZG, et al. Evaluation of platelet-rich plasma and fibrin matrix to assist in healing and repair of rotator cuff injuries: a systematic review and meta-analysis. Clin Rehabil. Feb 2017;31(2):158-172. PMID 26928856
50. Randelli PS, Stoppani CA, Santarsiero G, et al. Platelet-Rich Plasma in Arthroscopic Rotator Cuff Repair: Clinical and Radiological Results of a Prospective Randomized Controlled Trial Study at 10-Year Follow-Up. Arthroscopy. Jan 2022; 38(1): 51-61. PMID 34052372
51. Kubota G, Kamoda H, Orita S et al. Platelet-rich plasma enhances bone union in posterolateral lumbar fusion: A prospective randomized controlled trial. Spine J. 2019 Feb;19(2). PMID 28735763
52. Carreon LY, Glassman SD, Anekstein Y, et al. Platelet gel (AGF) fails to increase fusion rates in instrumented posterolateral fusions. Spine (Phila Pa 1976). May 1 2005; 30(9): E243-246; discussion E247. PMID 15864142
53. Tsai CH, Hsu HC, Chen YJ, et al. Using the growth factors-enriched platelet glue in spinal fusion and its efficiency. J Spinal Disord Tech. Jun 2009;22(4):246-250. PMID 19494743
54. Everts PA, Devilee RJ, Brown Mahoney C, et al. Exogenous application of platelet-leukocyte gel during open subacromial decompression contributes to improved patient outcome. A prospective randomized double-blind study. Eur Surg Res. 2008;40(2):203-210. PMID 17998780
55. Shu H, Huang Z, Bai X, et al. The Application of Platelet-Rich Plasma for Patients Following Total Joint Replacement: A Meta-Analysis of Randomized Controlled Trials and Systematic Review. Front Surg. 2022; 9: 922637. PMID 35860197
56. American Academy of Orthopaedic Surgeons. Management of Osteoarthritis of the Knee (Non-Arthroplasty). 2021; https://www.aaos.org/globalassets/quality-and-practice-resources/osteoarthritis-of-the-knee/oak3cpg.pdf. Accessed 5/21/24
57. American Academy of Orthopaedic Surgeons A. Management of Osteoarthritis of the Hip - Evidence-Based Clinical Practice Guideline. 2017; https://www.aaos.org/globalassets/quality-and-practice-resources/osteoarthritis-of-the-hip/oa-hip-cpg_6-11-19.pdf Accessed 5/21/24.

58. American Academy of Orthopaedic Surgeons. Management of Osteoarthritis of the Hip: Evidence-Based Clinical Practice Guideline. 2017; Report Title (aaos.org). Accessed 5/21/24
59. National Institute for Health and Care Excellence (NICE). Autologous blood injection for tendinopathy [IPG438]. 2013; https://www.nice.org.uk/guidance/ipg438 Accessed 5/21/24.
60. National Institute for Health and Care Excellence. Autologous blood injections for plantar fasciitis [IPG437]. 2013; https://www.nice.org.uk/guidance/ipg437 Accessed 5/21/24.
61. National Institute for Health and Care Excellence (NICE). Platelet-rich plasma injections for knee osteoarthritis [IPG491]. 2019; https://www.nice.org.uk/guidance/ipg637 Accessed 5/21/24.
62. FDA U.S. Food and Drug Regen Lab https://www.fda.gov/media/159770/download?attachment accessed 7/29/24

The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through 5/21/24, the date the research was completed.

Joint BCBSM/BCN Medical Policy History

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
5/1/16	2/16/16	2/16/16	Routine maintenance Topic previously addressed on policy, "Recombinant and Autologous Platelet-Derived Growth Factors as a Treatment of Wound Healing and Other Miscellaneous Conditions."
5/1/17	2/21/17	2/21/17	Routine maintenance
11/1/17	8/15/17	8/15/17	Routine maintenance
11/1/18	8/21/18	8/21/18	Routine maintenance
11/1/19	8/20/19		Routine maintenance
7/1/20	4/14/20		Code update, added C1734
7/1/21	4/20/21		Routine maintenance Ref 7,12,13,14,15,18,19,20,30,31, 32,43,50,51,52 added
11/1/21	8/17/21		Routine maintenance Ref 21,23,31,33,34,49 added
11/1/22	8/16/22		Routine maintenance Ref 7,8,18,26,36,38,47,56,58,63,65 added (ls)
11/1/23	8/15/23		Routine maintenance (jf) • Vendor Managed: Turning Point • Removed ref 13,14,15,41 • Added new ref: 7,17,39,42,43,61
11/1/24	8/20/24		Routine maintenance (jf) Vendor Managed: NA Removed ref:11,12,13,14,16,42,62

Next Review Date: 3rd Qtr, 2025

BLUE CARE NETWORK BENEFIT COVERAGE
POLICY: ORTHOPEDIC APPLICATIONS OF PLATELET-RICH PLASMA

I. Coverage Determination:

Commercial HMO (includes Self-Funded groups unless otherwise specified)	Not covered
BCNA (Medicare Advantage)	See Government Regulations section.
BCN65 (Medicare Complementary)	Coinsurance covered if primary Medicare covers the service.

II. Administrative Guidelines:

- The member's contract must be active at the time the service is rendered.
- Coverage is based on each member's certificate and is not guaranteed. Please consult the individual member's certificate for details. Additional information regarding coverage or benefits may also be obtained through customer or provider inquiry services at BCN.
- The service must be authorized by the member's PCP except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Services must be performed by a BCN-contracted provider, if available, except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Payment is based on BCN payment rules, individual certificate and certificate riders.
- Appropriate copayments will apply. Refer to certificate and applicable riders for detailed information.
- CPT - HCPCS codes are used for descriptive purposes only and are not a guarantee of coverage.